The American Journal of Medicine



The American Journal of Medicine

Editor: Alexander B. Gutman, M.D.

Professor of Medicine

COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK DIRECTOR, DEPARTMENT OF MEDICINE, THE MOUNT SINAI HOSPITAL, NEW YORK

Assistant Editors: Mortimer E. Bader, M.D. and Richard A. Bader, M.D. THE MOUNT SINAI HOSPITAL, NEW YORK

ADVISORY BOARD

DAVID P. BARR, M.D. Professor Emeritus of Medicine CORNELL UNIVERSITY MEDICAL COLLEGE NEW YORK

A. McGehee Harvey, M.D. Professor of Medicine JOHNS HOPKINS UNIVERSITY, SCHOOL OF MEDICINE BALTIMORE

ARTHUR L. BLOOMFIELD, M.D. Professor Emeritus of Medicine SCHOOL OF MEDICINE, STANFORD UNIVERSITY SAN FRANCISCO

WALTER L. PALMER, M.D. Professor of Medicine UNIVERSITY OF CHICAGO, SCHOOL OF MEDICINE CHICAGO

ASSOCIATE EDITORS

S. Howard Armstrong, Jr., M.D., Chicago PAUL B. BEESON, M.D., New Haven J. RUSSELL ELKINTON, M.D., Philadelphia PETER H. FORSHAM, M.D., San Francisco ROBERT M. KARK, M.D., Chicago WILLIAM S. McCann, M.D., Rochester, N. Y. John V. Taggart, M.D., New York

GEORGE R. MENEELY, M.D., Nashville CARL V. MOORE, M.D., St. Louis JACK D. MYERS, M.D., Pittsburgh ROBERT E. OLSON, M.D., Pittsburgh DEWITT STETTEN, JR., M.D., Bethesda

GEORGE W. THORN, M.D., Boston

The American Journal of Medicine is published monthly by The American Journal of Medicine, Inc., 11 East 36th Street, New York 16, N.Y. Yearly Subscription, \$12.00 U.S.A.; \$13.00 Canada; \$16.00 Foreign, including Latin-American countries, Single Numbers \$2.00; Symposium Numbers \$4.00. Second-class postage paid at New York, N.Y. and at additional mailing offices, November, 1958—Volume XXV, No. 5. Copyright © 1958, by The American Journal of Medicine, Inc. No part of the contents of this publication may be reproduced or distributed without the express written consent of the publishers.

Manuscripts: All manuscripts should be typewritten double space and addressed to the Editorial Office of the Journal, 11 East 36th St., New York 16, N. Y. The top should be indicated on the back of each photograph. Style for bibliography: Doe, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

Change of address must reach us one month preceding month of issue.

ADVERTISING REPRESENTATIVES

New York: Pliny A. Porter, Parker D. Brewer, Howard S. Schultz, Ronald P. Davis
—MUrray Hill 3-2980



Chicago: R. H. Andrew, C. P. Haffner -FRanklin 2-3861



protection against angina pectoris

in every walk of life



Peritrate® 20 mg. (bran pentaerythritol tetranitrate)

the accepted basic therapy in the treatment of coronary disease

- · reduces the frequency and severity of attacks
- · increases exercise tolerance
- · lowers nitroglycerin dependence
- · improves abnormal EKG findings

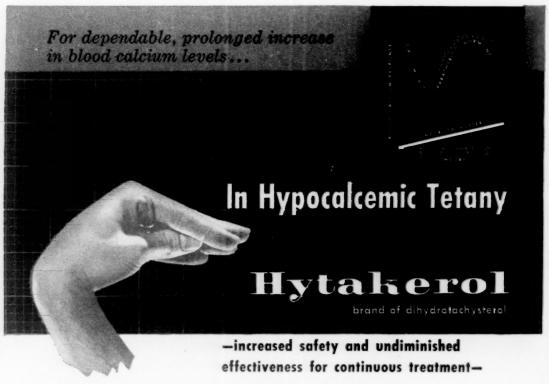
to relieve the acute attack

Peritrate with Nitroglycerin

replaces ordinary nitroglycerin in the patient taking Peritrate (not meant to replace Peritrate)

- · provides immediate relief of pain
- · automatically supplies an increased level of Peritrate for additional protection during the stress period





Since hypocalcemic tetany—usually the result of parathyroid deficiency—may require treatment for years, effective oral therapy with Hytakerol is superior to other methods.

Hytakerol increases absorption of calcium from the intestine and can be taken with undiminished effectiveness, indefinitely.

For prophylaxis following thyroidectomy and for chronic hypoparathyroidism, "... dihydrotachysterol... has proved to be the most valuable remedy..."

"Dihydrotachysterol...
is of great therapeutic value
in most cases of both
normocalcemic and
hypocalcemic tetany."²

Winthrop LABORATORIES NEW YORK 18, N. Y.

- Grollman, Arthur: Essentials of Endocrinology. Philadelphia, J.B. Lippincott Co., 2nd ed., 1947, p. 269.
- Sandock, Isadore: Tetany and ovarian function. J.A.M.A., 160:659, Feb. 25, 1956.

Hytakerol, trademark reg. U.S. Pat. Off.

DOSAGE: Orally from 3 to 10 cc. (or from 6 to 20 capsules) daily until tetany is relieved; weekly maintenance dose from 1 to 7 cc. (or from 2 to 14 capsules) depending upon the blood and urine calcium levels. From 10 to 15 Gm. calcium lactate or gluconate should be given daily as supplement through the period of therapy.

SUPPLIED: Hytakerol in Oil, bottles of 15 cc.

Hytakerol Capsules (each equivalent to 0.5 cc.), bottles of 50.

Chvostek's Sign—
Tonic contraction of the facial muscles results from tapping the facial nerve as it issues from the stylomastoid foramen—one of the diagnostic indications of hypocalcemic tetany.

The American Journal of Medicine

Vol. XXV NOVEMBER, 1958 No. 5

CONTENTS

Symposium on Nutrition in Internal Medicine	
Introduction to a Symposium on Nutrition in Internal Medicine John B. Youmans	659
Nutrition in Internal Medicine	662
The Physiologic Role of Vitamins	666
Some Clinical Aspects of Vitamin B Deficiencies W. H. Sebrell, Jr.	673
Nutritional Anemias with Especial Reference to Vitamin B ₁₂ Grace A. Goldsmith	680
Diet in the Treatment of Liver Disease	690
Some Aspects of Nutrition and the Kidney ROBERT M. KARK	698
Dietary Management of Diabetes Mellitus Herbert Pollack	708
Experimental Epidemiology of Chronic Sodium Chloride Toxicity and the Protective Effect of Potassium Chloride. George R. Meneely and Con O. T. Ball	713
Vitamin B ₁₂ Requirement of Adult Man WILLIAM J. DARBY, E. B. BRIDGFORTH, JEAN LE BROCQUY, SAM L. CLARK, JR., JOSE DUTRA DE OLIVEIRA, JOHN KEVANY, WILLIAM J. McGANITY AND CARLOS PEREZ	726
Clinical Studies	
Kinetocardiographic Changes as the Result of Mitral Commissurotomy E. E. Eddleman, Jr.	733
On the basis of an admittedly small experience, the author undertakes to evaluate the place of kine-tocardiography, a rather neglected method of analysis, in the selection of patients for mitral commissurotomy and in evaluation of the results obtained. It is pointed out that the method does permit a fairly direct estimation of right ventricular predominance or hypertrophy, and reflects the movements of ventricular contraction and relaxation before and after surgical intervention. In	

Contents continued on page 5

which patients
with noncalculous
gallbladder
disease
should undergo
surgery?

Essentially those who are not relieved by a prolonged trial period of medical management. Source-Lichtenstein, M. E.: GP 16:114 (Oct.) 1957.

for medical, preoperative, postoperative management of biliary disorders

"therapeutic bile"

DECHOLIN® and DECHOLIN SODIUM®

corrects biliary stasis

Hydrocholeresis with DECHOLIN produces abundant, thin, free-flowing, therapeutic bile. This flushes thickened bile, mucous plugs and debris from the biliary tract.



AMES COMPANY, INC.

Elkhart, Indiana
Ames Company of Canada Ltd.
Toronto

44731

AN AMES
CLINIQUICK
CLINICAL BRIEFS

FOR MODERN PRACTICE

CONTENTS continued - November 1958

VOLUME TWENTY-FIVE	V	0	1.	U	M	E	T	W	E	N	T	Y	-	F	I	V	E
--------------------	---	---	----	---	---	---	---	---	---	---	---	---	---	---	---	---	---

NUMBER FIVE

some cases mitral valvulotomy resulted in reversion of the kinetocardiogram to normal, and in such instances the clinical result was highly satisfactory. In others not associated with kinetocardiographic changes toward normal, clinical improvement, if it did occur, proved to be of short duration.

A Quantitative Abnormality in Serum Mucoproteins in the Marfan Syndrome

HABEEB BACCHUS 744

Marfan's syndrome is considered to reflect an inborn error in some as yet unidentified segment of connective tissue metabolism, a view which prompted examination of the serum mucoprotein levels in this disorder. The levels were found to be significantly reduced in relation to normal control subjects of equivalent age. This interesting observation deserves further exploration.

Transitory Congenital Neutropenia: A New Syndrome. Report of Two Cases Mario Stefanini, Rose H. Mele and David Skinner 749

Two well studied cases of transitory congenital neutropenia, presumably due to transplacental passage of a neutropenic factor, are described. The mothers and newborn infants both had leukopenia associated with bone marrow hyperplasia and maturation arrest of the granulocytic series; in one instance a leuko-agglutinin could be demonstrated in the maternal blood. The significance of these findings is interestingly discussed.

Review

Echinococcus Disease in the United States Arnold M. Katz and Chia-Tung Pan 759

Except in Alaska, the problem of echinococcus disease is not as important in the United States as in some other countries, nevertheless it appears in immigrants often enough (occasionally also is indigenously acquired) to warrant awareness of the differential diagnosis. The current status is admirably reviewed in this article, which considers both E. granulosus and E. multilocularis infections of special interest and the evaluation of available diagnostic procedures. This is an account of a case of echinococcosis contracted in Massachusetts.

Case Reports

Phosphate Diabetes. A Case Study of Osteomalacia

BOY FRAME AND RICHMOND W. SMITH, JR. 77:

A difficult problem in the differential diagnosis of "vitamin D-resistant osteomalacia," carefully studied and informatively discussed.

Paradoxical Embolism with Renal Failure Caused by Occlusion of the Renal Arteries Thomas J. Gill, III and Gustave J. Dammin 780

An interesting case and account of paradoxical embolism.

Contents continued on page 7



is the solid base line for successful therapy



Raudixin "lowers blood pressure and slows the pulse rate much more efficiently than the barbiturates.... It is not habit-forming and is synergistic with all other known hypotensive drugs."*

Raudixin helps you relieve pressureson your patients

Raudixin "relieves anxiety and tension, particularly the tension headache of the mild hypertensive patient, better than any other drug."*

RAUDIXIN..."is the best symptom reliever."*

In mild to moderate cases, Raudixin is frequently sufficient.

Base line therapy with Raudixin permits lower dosage of more toxic agents. The incidence and side effects of these agents are minimized. Diuretics often potentiate the antihypertensive effect of Raudixin.

SQUIBB



Squibb Quality-the Priceless Ingredient

CONTENTS continued-November 1958

V	O	L	U	M	E	T	W	E	N	T	Y	-	F	I	V	E
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

NUMBER FIVE

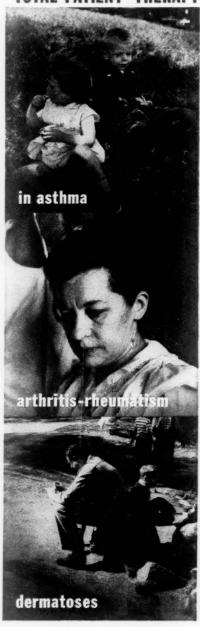
Unusual Manifestations in a Case of Relapsing, Nodular, Febrile Panniculitis (Weber-Christian Disease). Leonard M. Goldberg and Leonard W. Ritzmann	788
An instructive case.	
Pulmonary Infiltration with Eosinophilia and the Alveolar-Capillary Block Syndrome Frederic Eldridge	796
A patient with diffuse eosinophilic infiltration of the lung (Löffler's syndrome) presented the classic clinical and physiological findings of the alveolar-capillary block syndrome, thus adding another etiological basis for this syndrome. As the pulmonary infiltration cleared up, the evidences of impaired diffusion disappeared.	
Farmer's Lung. Report of Two Cases in Which Lung Biopsies Were Performed	
ROBERT S. TOTTEN, DAVID H. S. REID, HARVEY D. DAVIS AND THOMAS J. MORAN	803
A graphic description of a distinct disorder which, as the authors suggest, is probably more wide- spread than is now appreciated and should be better known.	
Chiari's Network LLOYD S. RALSTON AND WALTER A. WASDAHL An anomaly of unusual interest is well described.	810
Pseudoaortic Stenosis Produced by Ventricular Hypertrophy	

Seudoaortic Stenosis Produced by Ventricular Hypertrophy
BERNARD A. BERCU, GERALD A. DIETTERT, WILLIAM H. DANFORTH,
ERNEST E. PUND, JR., ROBERT C. AHLVIN AND ROBERT R. BELLIVEAU 814
A case of unusual interest.

MORE EFFICIENT THAN PREDNI-STEROIDS ALONE ATARAXO

prednisolone-hydroxyzine

'TOTAL PATIENT' THERAPY



EFFECTIVELY CONTROLS anxiety-tensioninduced exacerbations and emotional factors through the safe tranquilizer and musclerelaxant1 effects of hydroxyzine. Potentiates the action of prednisolone, markedly improving degree of response, sometimes doubling dosage efficiency, and permitting lower dosages.2-4 The unique antisecretory action⁵ of hydroxyzine also minimizes corticoidinduced gastric reactions.

- Hutcheon, D. E., et al.: Paper presented at Am. Soc. Pharmacol. & Exper. Therap., Nov. 8-10, 1956, French Lick,
- 2. Johnston, T. G., and Cazort, A. G.: Clin. Rev. 1:17, 1958. 3. Warter, P. J.: J. M. Soc. New Jersey 54:7, 1957.
- 4. Individual Case Reports to Medical Dept., Pfizer
- 5. Strub, I. H .: To be published.

SUPPLIED:

ATARAXOID 5.0

scored green tablets, 5.0 mg. prednisolone and 10 mg. hydroxyzine hydrochloride, bottles of 30 and 100.

ATARAXOID 2.5

scored blue tablets, 2.5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride, bottles of 30 and 100.

ATARAXOID 1,0

scored orchid tablets, 1.0 mg. prednisolone and 10 mg. hydrox-yzine hydrochloride, bottles of 100.



PFIZER LABORATORIES

Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York

ess:

Clinically confirmed in over 2,500 documented case histories1,3

CONFIRMED EFFICACY

- Deprol ▶ acts promptly to control depression without stimulation
 - restores natural sleep
 - reduces depressive rumination and crying

DOCUMENTED SAFETY

Deprol is unlike amine-oxidase inhibitors

- does not adversely affect blood pressure or sexual function
- causes no excessive elation
- produces no liver toxicity
- does not interfere with other drug therapies

Deprol is unlike central nervous stimulants

- ▶ does not cause insomnia
- produces no amphetamine-like jitteriness
- does not depress appetite
- ► has no depression-producing aftereffects
- can be used freely in hypertension and in unstable personalities

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: Each tablet contains 400 mg. meprobamate and 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl).

Supplied: Bottles of 50 scored tablets.

-Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) 1. Alexander, L.: Chemotherapy of depression hydrochloride. J.A.M.A. 166:1019, March 1, 1958. 2. Current personal communications; in the files of Wallace Laboratories.



Literature and samples on request WALLACE LABORATORIES, New Brunswick, N. J.

in the management of the "symptom-complex" constipation

- difficult-to-pass stools
- infrequent defecation due to inadequate peristalsis inadequate bulk
- or a combination of these symptoms

for soft, easy-to-pass stools

Colace

Dioctyl sodium sulfosuccinate, Mead Johnson

for predictable, yet gentle peristalsis

Peri-Colace

Dioctyl sodium sulfosuccinate and anthraquinone derivatives from cascara, Mead Johnson

new

to provide bulk in the intestine...not in the stomach1

Celginace

Calcium and sodium alginates and dioctyl sodium sulfosuccinate, Mead Johnson

tablets

granules

Celginace provides smooth, nonirritating 'hydrasorbent' bulk in the intestine, where bulk is needed. This avoids bloating, depressed appetite and discomfort as frequently occurs with bulking agents, such as psyllium derivatives or methyl cellulose, that hydrate in the stomach. And because of superior water absorption and retention, Celginace provides an effective bulk in a dosage of only one to three tablets daily.



new

a comprehensive approach to the relief of constipation

Combinace

Calcium and sodium alginates, dioctyl sodium sulfosuccinate and anthraquinone derivatives from cascara, Mead Johnson

tablets (B)

granules

When the patient presents a complex of symptoms, and combined therapy is indicated, Combinace provides (1) smooth, nonirritating, 'hydrasorbent' bulk of alginates, (2) the predictable, yet gentle peristaltic stimulation of Peristim* (3) the moistening action of Colace.

As a service to you in instructing patients, "Advice on Constipation" leaflets are available.

*Standardized. preparation of anthraquinone derivatives from cascara sagrada, Mead Johnson

 Mulinos, M. G., and Jerzy Glass, G. B.: Gastroenterology 24: 385-393 (May. Aug.) 1953.

UNEXCELLED ADVANTAGES ... IN BASIC DIURETIC REGIMENS

bicarbonate-regulating diuretic

Acetazolamide Lederle

HOW DIURETH

Advantages of DIAMOX in single-drug diuresis

DIAMOX - operating through the well-understood mechanism of · PREMENSTRUAL bicarbonate transport regulation-provides ample, prolonged diuresis in the great majority of patients.

DIAMOX is virtually nontoxic...has not caused renal or gastric irritation . . . has no pronounced effect on blood pressure. It is rapidly excreted, does not accumulate in the body, permits convenient dosage adjustment, allows unbroken sleep. Small, tasteless, easy-to-take tablets... usual dosage, only one a day.

Advantages of DIAMOX in intensive, two-drug diuresis

When intensive diuresis must be maintained, DIAMOX, alternated with an agent for regulation of chloride transport, has proved a regimen of choice. Through dual bicarbonate-chloride regulation, it produces maximal sodium-water excretion with minimal distortion of serum electrolyte patterns, greater patient comfort, lessened risk of induced drug resistance.

- CARDIAC EDEMA
- TENSION
- EDEMA OF PREGNANCY
- OBESITY
- ADVANCED CONGESTIVE **HEART FAILURE**
- REFRACTORY TOXEMIA OF PREGNANCY

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

*Reg. U. S. Pat. Off.

Lederle

MILK-LIKE



congestive

BECKER, M. C., Simon, F. and Bernstein, A.: J. Newark Beth Israel Hosp. 9:58 (January) 1958.

"On chlorothiazide the response was striking with . . . improvement in cardiac status and loss of toxic symptomatology. . . . One of the most important effects of the potent oral diuretic was the smooth continuous diuresis. There was less fluctuation in the weight . . . marked diminution in the number of acute episodes of congestive heart failure such as paroxysmal dyspnea and pulmonary edema. . . . [DIURIL] appeared as potent a diuretic as parenteral mercurials and indeed in some patients it was effective when parenteral mercurials failed. . . . We have encountered no patient who once responsive to chlorothiazide later developed resistance to it."

DOSAGE: one or two 500 mg. tablets DIURIL once or twice a day.

SUPPLIED: 250 mg. and 500 mg. scored tablets DIURIL (chlorothiazide); bottles of 100 and 1,000.

MERCK SHARP & DOHME Division of MERCK & CO., INC., Philadelphia 1, Pa. MSD



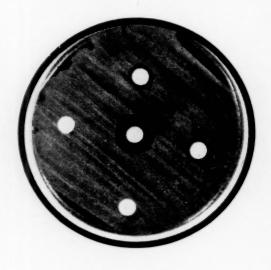
failure

markedly relieves pulmonary. edema



ANY INDICATION FOR DIURESIS IS AN IN

on the problem of antibioticresistant bacteria



A POINT OF VIEW IN '55 "At this time, it appears that the problem of antibiotic-resistant bacteria is the greatest fear in the future with chronic infections of the urinary tract..."

A POINT OF FACT IN '58 "... This prediction has proved to be correct for both gram-positive and gram-negative organisms."²

...WITH ONE NOTABLE EXCEPTION "... studies indicate that microorganisms, in vitro and in vivo, do not appear to develop resistance to FURADANTIN."3

for acute and chronic genitourinary tract infections

FURADANTIN

brand of nitrofurantoin

AVERAGE FURADANTIN DOSAGE: In acute, complicated or refractory cases and in chronic infections—100 mg. q.i.d., with meals and with food or milk on retiring. REFERENCES: 1. Flippin, H. F.: Virginia M. Month. 82:435, 1955. 2. Caswell, H. T., et al.: Surg. Gyn. Obst. 106:1, 1958. 8. Nesbitt, R. E. L., Jr., and Young, J. E.: Obst. Gyn., N. Y. 10:89. 1957.

in 7 years—negligible development of bacterial resistance with FURADANTIN

NITROFURANS...a new class of antimicrobials... o, moreover antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

For dietary management of serum cholesterol..

Mazola[®] Corn Oil

... a natural food and the only readily available vegetable oil made from golden corn

... rich in important unsaturated fatty acids, contains 56% linoleic acid

EASY AND PLEASANT TO ADMINISTER

Mazola Corn Oil, a highly palatable natural food, can easily be included as part of the everyday meals...simply and without seriously disturbing the patient's usual eating habits.

EFFECTIVE

Extensive recent clinical findings now show that serum cholesterol levels tend to be lower when an adequate amount of Mazola Corn Oil is part of the daily meals . . . high levels are lowered...normal levels remain normal.

PREFERRED

Nutrition authorities commonly recommend that from one-third to one-half of the total fat intake should be of the unsaturated type, whenever serum cholesterol control is a problem. The high content of important unsaturated fatty acids in Mazola, plus its other desirable characteristics, make it the oil of choice.

UNMATCHED QUALITY

A superlative cooking oil, a de-licious salad oil, clear, bland and odorless...adequate amounts of Mazola can be eaten daily as a natural food in a wide variety of salad dressings as well as in cooked, fried and baked foods.



Prepared as a special service for Physicians by Corn Products Co.

oupon for ordering:

Available FREE	LINOLEIC ACID Sitosterois	approximately: 7.4 Gm. 130 mg. 15 mg. 126 acids
		Please use this c
"UNIAPURATED PRITE AND MERITH CHOLESTERIA"	LATEST LITERATURE REVIEW	Medical Department Corn Products Comps 17 Battery Place, New
	"Unsaturated Fats and Serum Cholesterol"	Please send me a free copy book, "Unsaturated Fats and

Medical Department
Con Daylor
Corn Products Company
17 Battery Place, New York 4, N. Y.

y of your latest reference book, "Unsaturated Fats and Serum Cholesterol."

Name-Address_

_Zone__State_ Technical Pamphiet, "Facts about MAZOLA Corn Oil" also available. Provides technical information on chemical and physical properties. Check here if you wish a copy of this pamphlet.

A	comp	prehensive concepts.	revie	ew of	recent	res	earch	find	ings	and
CI	arrent	concepts.	This	book	covers	the	follor	ving	subj	ects.
-	-									

- The effect of different dietary fats on serum cholesterol
- The nature of the active components in vegetable oils.
- 4. Suggestions for practical diets.

PREVENT both cause and fear of ANGINA ATTACKS

"In diagnosis and treatment [of cardiovascular diseases]
...the physician must deal with both the emotional and
physical components of the problem simultaneously."

The addition of Miltown to PETN, as in Miltrate, "...appears to be more effective than [PETN] alone in the control of coronary insufficiency and angina pectoris."

1. Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card. 1:395, March 1958. Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology 8:504, Dec. 1957.

NEW dovetailed therapy combines in ONE tablet



trat

proven safety for long-term use

prolonged relief from anxiety and tension with

The original meprobamate, discovered and introduced by Wallace Laboratories sustained coronary vasodilation with

pentaerythritol tetranitrate a leading, long-acting nitrate

Miltrate is recommended for prevention of angina attacks, not for relief of acute attacks.

Supplied: Bottles of 50 tablets.

Each tablet contains: 200 mg. Miltown + 10 mg. pentaerythritol tetranitrate.

Usual dosage: 1 or 2 tablets q.i.d. before meals and at bedtime.

Dosage should be individualized.

For clinical supply and literature, write Dept. 26E

*WALLACE LABORATORIES, New Brunswick, N. J.



for everyday pain control . . .

for your many patients requiring potent analgesia but not an injected narcotic

Proved by extensive evaluation^{1,2,3} in 1998 patients in diverse areas of medicine and surgery, including:

arthritis, bursitis, early metastatic carcinoma, fibrositis, grippe, herpes zoster, ligamental strain, low back pain, menstrual pain, myalgia, myositis, neuritis, pleurisy, postoperative pain, postpartum pain, sciatica, trauma, dental pain

- · exclusive Wyeth non-narcotic analgesic plus anti-inflammatory action
- o prompt, potent action—as potent as codeine
- documented effectiveness and safety^{1,2,3}

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.



1. Cass, L.J., et al.: J.A.M.A. 166:1829 (April 12) 1958. 2. Batterman, R.C., et al.: Am. J. M. Sc, 234:413 (Oct.) 1957. 3. Medical Department, Wyeth: Final Report on the Clinical Evaluation of Zactirin.





Metabolic demands increase when the body is subjected to surgical procedures, burns, fractures and illness. Under such circumstances, restitution of depleted vitamin reserves will accelerate body repair. Stresscaps provide essential water-soluble vitamins in a professionally accepted formulation.

STRESSCAPS IN STRESS

- Infection Physiologic Trauma Endocrine Dysfunction
- · Emotional Stress · Pre- and Postoperatively

STRESSCAPS



LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK *Reg. U. S. Pat. Off.

Each Capsule Contains:

Thiamine Mononitrate (B₁)

	10 mg.
Riboflavin (B ₂)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B ₆)	2 mg.
Vitamin B ₁₂	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.
4 D 15	F F 15

Average Dose: 1-2 capsules daily.

A new concept in antihypertensive therapy: concomitant use of an improved ganglionic blocking agent ['Inversine'] and a new antihypertensive agent ['Diuril'] for smoother, simplified management of hypertension.

Longer Life for Hypertensives

In moderate, severe, and malignant hypertension, ganglionic blocking 'Inversine' often makes possible a lessening of cardiovascular-renal damage, regression of the basic disease, and prolongation of life.

"When employed under carefully controlled conditions with adequate attention to proper regulation of dosage, mecamylamine ['Inversine'] may be expected to reduce blood pressure effectively and to ameliorate various manifestations of hypertensive-cardiovascular disease. These include such symptoms as headache, dizziness, vertigo, hypertensive encephalopathy, cerebral or subarachnoid hemorrhage, retinopathy, cardiac hypertrophy and, in some cases, cardiac decompensation."

Council on Drugs, New and Nonofficial Remedies: Philadelphia, J. B. Lippincott Co., 1958, p. 285.

Now, concomitant use of a newly discovered antihypertensive agent ['Diuril' (Chlorothiazide)] has been found to enhance the hypotensive effect of 'Inversine'—while reducing the required dosage of 'Inversine' and often minimizing the serious side effects of ganglionic blockade.

'Inversine'

a greatly improved ganglionic blocking agent

Unlike the other ganglionic blocking agents, 'Inversine' is not a quaternary ammonium compound. It is a secondary amine, and has significant advantages over all other ganglionic blocking drugs:

- of the orally effective blocking agents, only 'Inversine' is completely and uniformly absorbed
- it provides predictable, reproducible effects with minimal day-to-day fluctuations in blood pressure response
- · 'Inversine' is effective in low dosage
- · permits convenient dosage schedules
- usefulness not limited by development of tolerance
- it has a gradual onset of effect, reducing the likelihood of sudden drops in blood pressure

Diuril'

new and unique antihy pertensive agent

- provides basic therapy to improve and simplify the management of hypertension
- · markedly enhances the effects of other antihypertensive agents
- · often reduces dosage requirement of ganglionic blocking agents and other antihypertensive agents below the level of serious side effects
- smooths out blood pressure fluctuations
- · added to other antihypertensive agents, is often effective in controlling blood pressure of even highly resistant cases
- · effectiveness not diminished by development of tolerance
- · well tolerated even at maximum therapeutic doses

DOSAGE RECOMMENDATIONS

New Patients

1. Initiate therapy with 'Diuril'

'Diuril' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. Adjust dosage of other agents

The dosage of other antihypertensive medication ('Inversine', reserpine, veratrum, hydralazine, etc.) is adjusted as

indicated by patient response.
'Inversine' is given in the same manner whether used with 'Diuril' or alone. Recommended initial dosage is 2.5 mg. twice a day, preferably after meals. May be increased

by 2.5 mg. at intervals of no less than two days until desired response is obtained. In severe or urgent cases, the increments may have to be larger or more frequent, with the largest dose given preferably at noon or in the evening. 'Inversine' is extremely potent and should always be titrated according to the patient's orthostatic blood pressure response.

. Adjust dosage of all medication

The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

Patients on 'Inversine' and/or other ganglionic blocking agents

1. Initiate therapy with 'Diuril'

'Diuril' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. Adjust dosage of ganglionic blocking agent

If the patient is established on a ganglionic blocking agent (e.g., 'Inversine') it should be continued, but the total daily dosage should immediately be reduced by as much as 25 to 50 per cent. This will reduce the serious side effects often

observed with ganglionic blockade.

If other antihypertensive agents are used, their dosage should be adjusted as indicated by patient response.

3. Adjust dosage of all medication

The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

Precautions: Side effects of 'Inversine' are essentially the same as those encountered with other ganglionic blocking agents. At the first sign of constipation, vigorous treatment must be initiated immediately since paralytic ileus may result if constipation is unchecked. Patients should be informed how to cope with postural hypotension should this occur. 'Inversine' is contraindicated in coronary insufficiency, organic pyloric stenosis and recent myocardial infarction.

Supplied: 'Inversine', tablets of 2.5 mg. and 10 mg. Bottles of 100. 'Diuril', tablets of 250 mg. and 500 mg. Bottles of 100 and 1000.

Inversir



MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

INVERSINE and DIURIL are trade-marks of MERCK & CO., INC.

Nove-the most videly prescribed translated translated to the second seco

in sustained release capsules

Meprospan*

Meprobamate P(Miltown*) capsules



 Meprobamate is more widely prescribed than any other tranquilizer. Source: Independent research organization; name on request.

230.

 Baird, H. W., III: A comparison of Meprospan (sustained action meprobamate capsule) with other tranquilizing and relaxing agents in children. Submitted for publication, 1958. Two capsules on arising last all day

Two capsules at bedtime last all night
relieve nervous tension on a sustained
basis, without between-dose interruption

"The administration of meprobamate in sustained action form [Meprospan] produced a more uniform and sustained action... these capsules offer effectiveness at reduced dosage."²

Dosage: 2 Meprospan capsules q. 12 h. **Supplied:** 200 mg. capsules, bottles of 30.

[®]WALLACE LABORATORIES, New Brunswick, N. J. who discovered and introduced Miltown[®]

Literature and samples on request

Cerofort

POTENTIATES TISSUE PROTEIN SYNTHESIS

Critically
essential L-lysine
with all the
important vitamins

Critically essential L-lysine with B vitamins

tablets

To speed convalescence in major surgery, illness, injury

Efficient protein synthesis depends upon an adequate take of proper proporti

of all the essential amino acids

Simultaneously. The biological value
of cereal proteins, which comprise 20% to

40% of total dietary proteins, is limited by a
relative deficiency of lysine. Cerofort supplies
ysiologic amounts of Lilysine to raise the body building
e of many cereals to that of high quality protein

appetite-stimulating B vitamins. Cerofort Tablets provide therapeutic sevels of all known essential vitamins. In order to obtain the optimal benefit of lysine supplementation administration with meals is essential

> DOSAGE: 1 Tablet t.i.d. with meals. Cerofort Tablets in bottles of 60.



DOSAGE: 1 tsp. t.i.d. with meals. Cerofort Elixir in bottles of 8 oz.

first with lysine

WHITE LABORATORIES, INC., Kenilworth, N. J.

elixir

To improve nutrition in the elderly, the adolescent, the growing child

to control both hyperacidity and hypermotility,

antisecretory-antispasmodic

Antrenyl, a potent antisecretory and antispasmodic, effectively relieves spasm, acidity and pain of the gastrointestinal tract and promotes healing of peptic ulcers. Of 70 patients whose condition (duodenal or gastric ulcer, spastic colon, ulcerative colitis, post-licostomy, functional discretes) had failed to respond adequately to other forms of therapy (antacids, sedatives, belladonns, atropine, other anticholinergics), 52 obtained satisfactory results with Antrenyl (74.3%). "The substitution of Antrenyl for other anticholinergic therapy constituted a distinct therapeutic advantage for this group of patients."

1. Notkin, L. J.: Canad. M.A.J. 78:385 (Oct. 1) 1988.

Supplied: TABLETS, 5 mg. (white, scored); bottles of 100, 500 and 1000. SYRUP, 5 mg. per 4-ml. teaspoon; bottles of 1 pint.

ANTRENYL® bromide (oxyphenonium bromide CIBA)

I B A SUMMIT, N. J. new orally potent narcotic analgesic

unsurpassed even for

- orally potent consistently gives profound relief
- minimal side effects

Additional information to physicians on request. Subject to Federal Narcotic Law. LERITINE is a trade-mark of Merck & Co., Inc.



MERCK SHARP & DOHME DIVISION OF MERCK & CO., Inc., PHILADELPHIA 1, PA.

FEWER ANGINAL ATTACKS. PROTECTS AGAINST PAIN NTROLS ANXIETY. PETNAND

EQUANITR





...THREATENED VITAMIN DEFICIENCY . PREVENT IT WITH

HIGH POTENCY VITAMIN-MINERAL SUPPLEMENT

Each MYADEC Capsule provides the
benefits of:
Vitamins:
Vitamin B ₁₂ crystalline
Vitamin B ₂ (riboflavin) 10 mg.
Vitamin B ₆ (pyridoxine hydrochloride) 2 mg.
Vitamin B ₁ mononitrate
Nicotinamide (niacinamide) 4 100 mg.
Vitamin C (ascorbic acid)150 mg.
Vitamin A . 44474 (7.5 mg.) 25,000 units
Vitamin D (25 meg.) 1,000 units
Vitamin E
(d-alpha-tocopheryl-acetate concentrate)

Minera	1	(0	;,					, ,)							
Iodine												()			
Manga	ric													()	
Cobalt															
Potassi														()	
Molybo															
Iron -															
Copper															
Zine .:															
Magnes	siu														
Calciur															
Phosph													(),(
Bottles				1 (



PARKE, DAVIS & COMPANY - DETROIT 32, MICHIGAN

NOSE COLD



HEAD COLD



WINTER



PHENAPHEN® PLUS

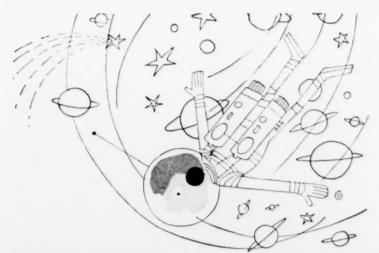
Phenaphen Plus is the physician-requested combination of Phenaphen, <u>plus</u> an antihistaminic and a nasal decongestant.

Available on prescription only.



each coated tablet contains: Phenaphen
Phenacetin (3 gr.) 194.0 mg.
Acetylsalicylic Acid (2½ gr.) . 162.0 mg.
Phenobarbital (¼ gr.) . . . 16.2 mg.
Hyoscyamine Sulfate . . . 0.031 mg.
plus
Prophogogyidamine Maleste

Prophenpyridamine Maleate . . 12.5 mg.
Phenylephrine Hydrochloride . 10.0 mg.



BRING HIM BACK FROM OUTER SPACE

to feed the inner man



With REDISOL (vitamin B_{12})—new zest for meals. Soluble REDISOL tablets (25, 50, 100, 250 mcg.) and cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) mix readily with liquids.

REDISOL is a trade-mark of Merck & Co., Inc.



MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

Unquestioned therapeutically

...long established clinically

SUSPENSION

(chocolate-flavored)

For the many bacterial infections that respond promptly to triple sulfonamide therapy, Trisem presents a preferred formula.

Each 5 cc. contains, in a pleasant, chocolate-flavored vehicle:

Sulfamerazine (microcrystalline) 0.167 Gm. (2 3/5 gr.)

Sulfadiazine (microcrystalline) 0.167 Gm. (2 3/5 gr.)

Sulfamethazine (microcrystalline) . . . 0.167 Gm. (2 3/5 gr.)

Each 5 cc. (1 tsp.) provides 0.5 Gm. total sulfonamides.

Each 15 cc. (1 tbsp.) provides 1.5 Gm. total sulfonamides.

ADVANTAGES

- wide patient acceptability
- unquestioned therapeutic value
- high index of safety

- broad antibacterial spectrum
- provides high blood levels promptly
- economical for the patient

Many physicians prefer to use the sulfonamides to control bacterial infections because resistant organisms rarely develop. Nor, as with some broad spectrum therapy, is there the complication of such after-effects as moniliasis.

PACKAGING: In pint and gallon bottles.

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE

New York

Kansas City

San Francisco



if you were in the rheumatoid arthritic's shoes,

Doctor...

wouldn't you want a steroid with a proved record of safety and success?

METICORTEN

you can count on rapid relief from pain, swelling and stiffness followed by functional improvement and maintained on an uncomplicated, low-dosage regimen with minimal chance of side effects† and without unexplained weight loss, anorexia, muscle cramps as reported with certain other corticoids†

†Round-table Discussion by Leading Investigators, San Francisco, Calif., June 20, 1958.

METICORTEN, 1, 2.5 and 5 mg. white tablets.

SCHERING CORPORATION . BLOOMFIELD, NEW JERSEY



OF EVERY AGING PATIENT

The combination of declining gonadal function and increased vulnerability to malnutrition conspire to accelerate the aging process. You can protect the aging patient by prescribing a "Clusivol" Geriatric capsule daily.

There are four important features of "Clusivol" Geriatric:

- 1. Vitamins -12 important nutritional supplements, notably vitamins A and D, the factors of the B complex, and vitamin C.
- 2. Minerals and trace elements -10 protective factors to ensure optimal blood and bone building.
- 3. Amino acids lysine and methionine, key amino acids usually lacking in finicky geriatric diets.
- 4. Gonadal steroids estrogen and androgen in small quantities to restore the integrity of the body mechanism.

Supplied: No. 294 - Capsules, bottles of 100 and 1,000.

"CLUSIVOL" GERIATRIC

potent nutritional elements with steroids



AYERST LABORATORIES . NEW YORK 16, N. Y. . MONTREAL, CANADA

this time; start with...

PREDNISONE, PARKE-DAVIS

or

THREE TO FIVE TIMES THE ACTIVITY OF CORTISONE OR HYDROCORTISONE.

supplied: PARACORT and PARACORTOL are available as 5-mg, and 2.5-mg

PARKE, DAVIS & COMPANY . DETROIT 32, MICHIGAN

*TRADEMARK

3018

a new type of effectiveness in depression and fatigue states

References

Lemere, F., and Lasater, J. H.: Am. J. Psychiat. 114:655 (Jan.) 1958.

Murphree, H. B., Jr.; Jenney, E. H., and Pfeiffer, C. C.: 2-Di-methylaminoethanol as a Central Nervous Sys-

a Central Nervous System Stimulant, Presented before Assoc. for Research in Nervous and Mental Disease, New York, Dec. 12-14, 1957. To be published.

Oettinger, L., Jr.: Presented before the American Encephalographic Society Meeting, Atlantic City, June 14, 1958.

To be published, Journal

of Pediatrics.

Anti Vepressant

p-acetamidobenzoic acid salt of 2-dimethylaminoethanol

The effects of 'Deaner' are unlike those of other energizers. After coming on gradually, effects are prolonged... free from hyperirritability, jitteriness or emotional tension... free from excessive motor activity...free from loss of appetite...free from elevation of blood pressure or heart rate ... free from sudden letdown on discontinuance of therapy.

Deaner'a totally New Molecule

has proved to be of value in the alleviation of a wide variety of emotional disturbances.1 It is indicated in

- chronic fatigue states
- mild depression
- chronic headache
- migraine
- neurasthenia
- behavior problems and learning defects in children

Deaner produces greater daytime energy, better ability to concentrate, and a more affable mood.2 It promotes sounder sleep.2 In children it enhances adaptability and lengthens attention span.3

Another



First NORTHRIDGE, CALIFORNIA

Dosage: Itablet (25 mg.)
Initially the morning tablets, daily in the morning tablets, to 3 tablets, the control of the control weeks or more of therapy.

"Deaner' is supplied 25

"Deaner' is containing than a sored tablets containing than a sored 2-dimethylaminoethan as the p-acetamidoben nol as the p-acetamidoben 201c acid salt.



FILIBON

offers your maternity patient full supplementation of the required vitamins and minerals, in addition to these important extras—

- · a new form of iron to minimize gastric irritation
- the prophylactic vitamins $B_{\rm 6}$ and K
- AUTRINIC* Intrinsic Factor Concentrate for effecttive B₁₂ absorption
- · important trace elements
- · a phosphorus-free formula

FILIBON . . fashioned for her

to keep her on her prescribed regimen

- · the attractive FILIBON Jar
- · a convenient dosage-just one a day
- a small, easy-to-swallow capsule—dry-filled for rapid absorption and freedom from unpleasant aftertaste

Each soft-shell FILIBON capsule contains:

municipal and a second and and		
Vitamin A 4,000 U.S.P. Units Vitamin D 400 U.S.P. Units	Folic Acid Ferrous Fumarate	1 mg. 90 mg.
Thiamine Mononitrate (B ₁) 3 mg.	Iron (as Fumarate) Fluorine (CaF ₂)	30 mg. 0.015 mg.
Pyridoxine (B ₆) 1 mg. Niacinamide 10 mg.	Copper (CuO)	0.15 mg.
Riboflavin (B2) 2 mg. Vitamin B12 with	Iodine (KI) Potassium (K2SO4)	0.01 mg. 0.835 mg.
AUTRINIC Intrinsic Factor Concentrate	Manganese (MnO ₂) Magnesium (MgO)	0.05 mg. 0.15 mg.
1/6 U.S.P. Oral Unit Ascorbic Acid (C) 50 mg.	Molybdenum (Na2MoO4, 2H2O)	0.025 mg.
Vitamin K (Menadione) 0.5 mg.	Zinc (ZnO) Calcium Carbonate	0.085 mg.

in the picture...during pregnancy

Filibon*



DOSAGE one or more capsules daily
SUPPLIED attractive re-usable bottles
of 100 capsules

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York *Reg. U. S. Pat. Off.





NOW... CONTROL VASCULAR AND NON-VASCULAR HEADACHE

WIGRAINE®

FOR VASCULAR HEADACHES

Wigraine provides rapid and complete relief of symptoms of migraine and other vascular headaches with just two tablets (or one rectal suppository) taken at the first sign of an attack.

Formula: Ergotamine tartrate, 1.0 mg.; caffeine, 100.0 mg.; 1-belladonna alkaloids, 0.1 mg.; acetophenetidin, 130.0 mg. Wigraine tablets in boxes of 20 and 100. Wigraine Rectal Suppositories in boxes of 12.

MEDACHE

FOR NON-VASCULAR HEADACHES

Medache provides safe analgesic-calmative action for relief of pain, anxiety, and allergic manifestations of tension and other non-vascular headaches.

Formula: Phenyltoloxamine dihydrogen citrate*, 44.0 mg. (equiv. phenyltoloxamine, 25.0 mg.); salicylamide, 150.0 mg.; phenacetin, 150.0 mg.; caffeine, 32.0 mg. In bottles of 100 tablets.

*U.S. Pat. No. 2,703,324

Send for samples and complete descriptive literature.



FOR THE CARDIAC CANDIDATE CAUGHT IN THE

SQUEEZE

AVOIDS THE THERAPEUTIC EX-TREMES OF PREVIOUS RESER-PINE AND RAUWOLFIA AGENTS

"DEPRESSION ACCOMPANIED BY ANXIETY...WAS NOT SEEN..." WITH THIS NEW ALKALOID OF RAUWOLFIA. OTHER UNDESIRABLE RAUWOLFIA-RESER-PINE REACTIONS ARE SELDOM ENCOUNTERED OR ARE MINOR IN DEGREE. 1-3 PRODUCES SIGNIFICANTLY MORE STABLE AND SUSTAINED CONTROL OF THE TENSION-HYPERTENSION COMPLEX.4 HIGHER DOSAGES MAY BE EMPLOYED WHERE INDICATED, WITH CONTINUED EXCELLENT TOLERATION.1-4 ALSO PREFERRED FOR THERAPY OF ACUTE ANXIETY STATES AND CHRONIC

MENTAL DISORDERS.4.5

Supplied: MODERIL Tablets—yellow, scored 0.25 mg. oval tablets, bottles of 100 and 500; salmon, scored 0.5 mg. oval tablets, bottles of 100.

Dosage: The recommended initial dosage is 0.5 mg. twice daily for two weeks, with reduction thereafter to a minimum maintenance dosage of 0.25 mg. once daily, for greater hypotensive effect after initial period, increase dosage cautiously by 0.25 mg. daily up to a maximum daily dosage of 2.0 mg. Prescribe after meals.



1 Moyer, J. H., et al.: A M.A. Arch. Int. Med. 96 530, 1955. 2. Moyer, J H., et al.: South. M. J. 50 499, 1957. 3. Smirk, F H., and McQueen, E. G.: Lancet 2.115, 1955. 4 Winton, S. S.: Internat. Rec. Med. 170.665, 1957. 5 Malamud, W., et al.: Am. J Psychiat 114:193,1957.



Division.

Chas Pfizer & Co., Inc. Brooklyn 6, New York

FOR THE CARDIAC CANDIDATE

LINODOXINE

Linoleic Acid (Essential Unsaturated Fatty Acid) and Pyridoxine HCI

REDUCES
ELEVATED
SERUM
CHOLESTEROL
LEVELS IN
A SUBSTANTIAL
MAJORITY OF
PATIENTS¹⁻⁵

PLEASANTLY ORANGE-FLAVORED EMULSION AVOIDS TASTE FATIGUE

EMULSION

bottles of 1 pint
Dosage:
1 tablespoonful t.i.d.

CAPSULES

bottles of 100 and 250 Dosage: 2 to 4 capsules t.i.d. before meals

1. Van Gasse, J. J., and Miller, R. F.: Current Concepts on the Etiology and Management of Atheroscierosis, Scientific Exhibit, A.M.A. Meet., June 3-5, 1957, New York, 2. Farquhar, J. W., and Sokolow, M.: Circulation 17:890, 1958.

3. Kinsell, L. W., et al.: Lancet 1:334, 1958.

4. Malmros, H., and Wigand, G.: Lancet 21, 1957, 5. Van Italile, T. B.: J. Am. Dietet. A. 34:248, 1958.

Pfizer

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York

adsorptive power

CLAYSORB

KAOLIN

CLAYSORB is 5 times as adsorptive as kaolin

When you prescribe Polymagma or Polymagma Plain to control diarrhea, you are prescribing adsorptive superiority. Both preparations contain Claysorb—a new intestinal adsorbent whose superiority over kaolin has been demonstrated in exhaustive studies.^{1,2,3}

For *bacterial* diarrhea, POLYMAGMA is bactericidal to many intestinal pathogens. It is soothing and protective to the irritated mucosa. It aids in the restoration of normal intestinal function. Highly effective, highly palatable.

For *nonbacterial* diarrhea, Polymagma Plain—same formula but without antibiotics.

Barr, M., and Arnista, E.S.: J. Am. Pharm. A. (Scient. Ed.) 46:493 (Aug.) 1957.
 Barr, M., and Arnista, E.S.: *Ibid.* 46:486 (Aug.) 1957.
 Barr, M.: *Ibid.* 46:490 (Aug.) 1957.

Polymagma®

Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb* (Activated Attapulgite, Wyeth) in Alumina Gel

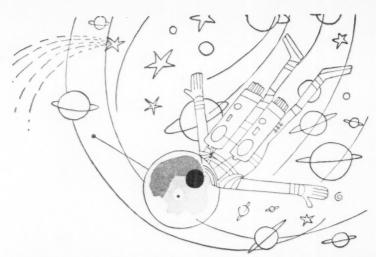




Philadelphia 1, Pa.



This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health



BRING HIM BACK FROM OUTER SPACE

to feed the inner man



With REDISOL (vitamin B_{12})—new zest for meals. Soluble REDISOL tablets (25, 50, 100, 250 mcg.) and cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) mix readily with liquids.

REDISOL is a trade-mark of Merck & Co., Inc.



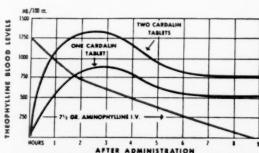
MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

A NEISLER RESEARCH PRODUCT



higher and more sustained theophylline blood levels... orally



(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11:301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100:309, 1950.)

CARDALIN

proven effective clinically whenever high blood levels of theophylline are desired. Cardalin contains two protective factors* to guard against the nausea, gastric irritation and vomiting which occasionally accompany a high oral dose of aminophylline.

*U. S. Patent No. 2,667,439

Each tablet contains:

Aminophylline 5.0 gr.
Aluminum hydroxide . . . 2.5 gr.
Ethyl aminobenzoate . . . 0.5 gr.
Also available as Cardalin-Phen
with ¼ gr. phenobarbital.

To serve your patients today—call your pharmacist for any additional information you may need to prescribe Cardalin. And for prescription economy, prescribe Cardalin in 50's.

Irwin, Neisler & Co. . Decatur, Illinois

Neisler

PMB-200

"Premarin" with Meprobamate

Each tablet contains 0.4 mg. "Premarin," 200 mg. meprobamate.

PMB ("Premarin" with Meprobamate) is an ideal preparation for the control of the menopausal syndrome when undue emotional stress is a complication. When these symptoms are relieved, therapy is resumed with "Premarin" alone.

Simple to prescribe as merely PMB

DMB 200 \$60 200 Sig. tab. Thid

Supply: No. 880, PMB-200, bottles of 60 and 500.

Cyerst ®

Also available

No. 881, PMB-400 ("Premarin" 0.4 mg. with meprobamate 400 mg.), bottles of 60 and 500.

AYERST LABORATORIES . NEW YORK 16, N. Y. . MONTREAL, CANADA

The <u>NEW</u> potency of "Premarin" with Meprobamate physicians requested

The combination of 0.4 mg. "Premarin" and 200 mg. meprobamate – a new potency – may be prescribed simply as PMB-200.

The new potency, PMB-200, enables you to attune therapy to the needs of your patients in the menopause who require extra relief from anxiety and tension, in addition to estrogen therapy. PMB-400 (0.4 mg. "Premarin" and 400 mg. meprobamate) continues to be available.

When emotional lability has been stabilized, and stress symptoms controlled, therapy may be continued with "Premarin" alone.

Write simply...

PMB-200

Ayerst Laboratories • New York 16, N.Y. • Montreal, Canada

"Premarin®" conjugated estrogens (equine)

Meprobamate licensed under U.S. Pat. No. 2,724,720

When anxiety and tension complicate HIGH
BLOOD
PRESSURE



Miltown

Miltown in addition to ganglionic blocking therapy resulted in subjective and objective improvement in 35 of 37 patients. On the antihypertensive agent alone, only 28 patients improved.¹

1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. 234: 150, Aug. 1957.

Literature and samples on request



The original meprobamate, discovered and introduced by WALLACE LABORATORIES, New Brunswick, N. J. CM-0792



HELPS PALSIED PATIENTS "LIVE AGAIN"

COGENTIN

METHANESULFONATE (BENZTROPINE METHANESULFONATE)

rated the best single drug for the palsied patient¹

- Well tolerated and markedly effective, COGENTIN "should be added to the treatment program of every patient with paralysis agitans." ²
- COGENTIN gives symptomatic relief in all types of parkinsonism—whether postencephalitic, idiopathic, or arteriosclerotic.
- COGENTIN provides highly selective action such as no other current drug affords.² It is often of benefit in rigidity, muscle spasm, even in severe tremor.³ The contracture of parkinsonism is relieved and posture is improved.³
- With the help of COGENTIN, therapy with tranquilizers can often be continued in patients in whom trembling would otherwise force reduction or withdrawal.⁴

As COGENTIN is long-acting, one dose daily may be sufficient.

Supplied: as 2 mg. quarter-scored tablets in bottles of 100 and 1000.

M. Clin. North America 38:485 (March) 1954.
 J.A.M.A. 162:1031,
 J.A.M.A. 156:680, 1954.
 Yale J. Biol. & Med. 28:308, 1955/56.





ROCHE

a pioneer in antimicrobial therapy now presents

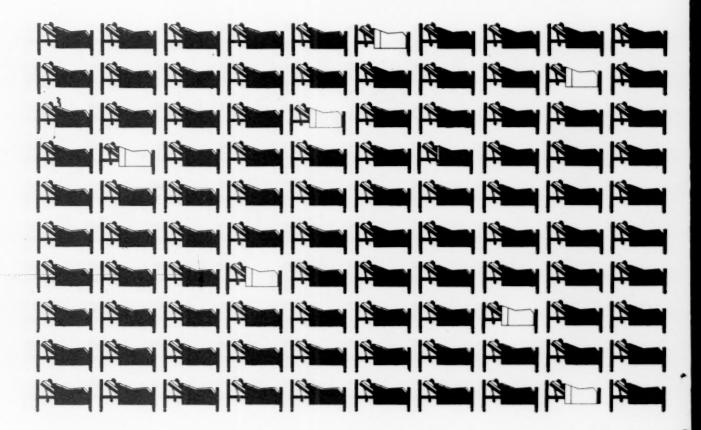
MADRIBON

a new development
in the control of systemic infections
particularly those of the respiratory tract.

MADRIBON

introduces new standards
of effectiveness and tolerance
characterized by
rapid, prolonged blood levels
and a basically different metabolism.

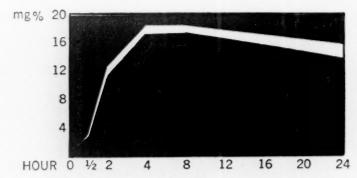
new MADRIBON



a superior chemotherapeutic agent

Rapid, prolonged blood levels

a characteristic of Madribon, assure prompt response and greater convenience of dosage.



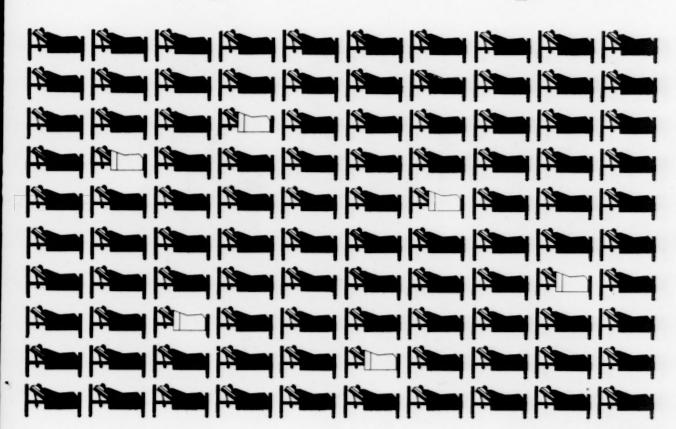
Average blood level after administration of a single 2 Gm dose of Madribon.

Excreted differently

Madribon differs from all previously known chemotherapeutic agents in that it is metabolized mostly as a glucuronide.

Glucuronide conjugate accounts for approximately 80 per cent of the Madribon urine level.

...already proved in 5000 patients



good or excellent response

poor response





each symbol represents 25 cases

Highly soluble

The glucuronide form of Madribon is exceptionally soluble - providing an important margin of therapeutic safety.



Solubility of Madribon in the urine: over 2000 mg/100 ml.



continued on next page

new

in systemic infections, particularly those of the upper respiratory tract

MADRIBON

is realistic therapy

Especially for "u.r.i." Madribon shows marked activity against a wide spectrum of gram-positive and gram-negative pathogens. Its greatest benefit, however, may well lie in the treatment of upper respiratory infections. In one representative study, "including acute pharyngitis, tonsillitis, otitis media and two cases of bacterial pneumonia...therapeutic results were satisfactory in the majority of cases with prompt defervescence and general clinical improvement together with a return of the white count to normal within two to four days."

"The use of Madribon was very simple and there were no side effects or toxic reactions." Madribon, though new, is already backed by extensive clinical experience. Based on completed case records presently on file with the Medical Department of Roche Laboratories, the incidence of side effects (such as nausea or dizziness) is only 1.3 per cent in more than 5000 Madribon-treated patients.

Usual Dosage (for mild to moderate infections):

ADULTS: 2 tablets (4 teaspoonfuls) initially followed by 1 tablet (2 teaspoonfuls) daily thereafter.

CHILDREN: Initially

Every 24 hours

20 pounds 1 teaspoonful (½ tablet) 40 pounds 2 teaspoonfuls (1 tablet) ½ teaspoonful (¼ tablet) 1 teaspoonful (½ tablet)

80 pounds 4 teaspoonfuls (2 tablets) 2 teaspoonfuls (1 tablet)
Therapy should be continued for 5 to 7 days or until patient is asymptomatic for at least 48 hours.

Pachages.

TABLETS: 0.5 Gm, double scored, monogrammed, gold colored—bottles of 30, 250 and 1000.

SUSPENSION: 0.25 Gm/teasp. (5 cc), custard flavored—bottles of 4 oz and 16 oz.

MADRIBONT-M.—2,4-dimethoxy-6-sulfanilamido-1,3-diazine

- wider spectrum
- · safer
- · more convenient
- · economical

1. S. Ross, Paper read at the Sixth Annual Antibiotic Symposium, Washington, D.C., Oct. 15-17, 1958.

2. W. A. Leff, Paper read at the New Jersey Chapter of the Am. Fed. Clin. Res., Newark, Sept. 17, 1958.



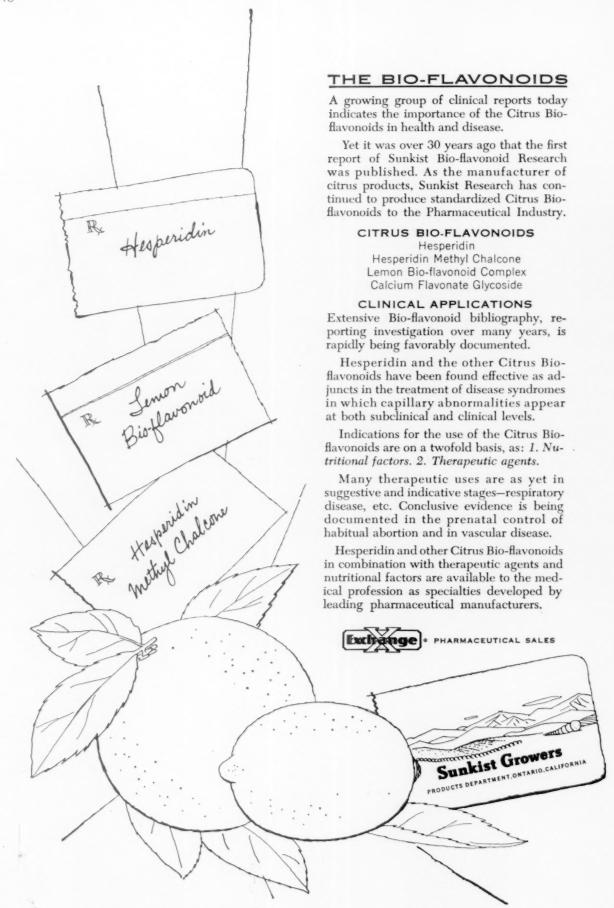
This patient's blood-pressure controlled for the first time without side effects

Remember this particular patient. He typifies the thousands of patients involved in a clinical investigation which promises to bring about a major change in rauwolfia therapy. The patient is being treated in a Massachusetts hospital. His blood pressure without treatment ranged up to 220/138; now for the first time, it is being maintained near normal without side effects. This dramatic case history is part of the story of a remarkable new antihypertensive agent **Singuscern**

coming as soon as sufficient supplies are available... from CIBA, world leader in hypertension research.



2/2608MM





House call: agitation

The acutely excited patient can be quickly calmed when SPARINE is on hand in the physician's bag. In both medical and mental emergencies, SPARINE quiets hyperactivity, encourages cooperation, and simplifies difficult management.

Sparine gives prompt control by parenteral injection and effective maintenance by the intramuscular or oral route. It is well tolerated.

Comprehensive literature supplied on request

Sparine HYDROCHLORIDE

Promazine Hydrochloride, Wyeth

INJECTION

TABLETS

SYRUP



"Much better-



-thank you, doctor"

COSA-TETRACYN*

GLUCOSAMINE-POTENTIATED TETRACYCLINE

CAPSULES

(black and white) 250 mg., 125 mg.

ORAL SUSPENSION

(orange-flavored) 125 mg. per tsp. (5 cc.), 2 oz. bottle NEW! PEDIATRIC DROPS

(orange-flavored) 5 mg. per drop, calibrated dropper, 10 cc. bottle

Proven in research

- 1. Highest tetracycline serum levels
- 2. Most consistently elevated serum levels
- **3.** Safe, physiologic potentiation (with a natural human metabolite)

And now in practice

- 4. More rapid clinical response
- 5. Unexcelled toleration

COSA-TETRASTATIN*

glucosamine-potentiated tetracycline with nystatin antibacterial plus added protection against monilial superinfection

CAPSULES (black and pink) 250 mg. Cosa-Tetracyn (with 250,000 u. nystatin)

ORAL SUSPENSION 125 mg. per tsp. (5 cc.) Cosa-Tetracyn (with 125,000 u. nystatin), 2 oz. bottle

COSA-TETRACYDIN*

glucosamine-potentiated tetracycline – analgesic – antihistamine compound

For relief of symptoms and malaise of the common cold and prevention of secondary complications

CAPSULES (black and orange) Each capsule contains: Cosa-Tetracyn 125 mg. • phenacetin 120 mg. • caffeine 30 mg. • salicylamide 150 mg. • buclizine HCl 15 mg.



Science for the world's well-being PFIZER LABORATORIES Division, Chas. Pfizer and Co., Inc. Brooklyn 6, New York

REFERENCES: 1. Carlozzi, M.: Ant. Med. & Clin. Therapy 5:146 (Feb.) 1958. 2. Welch, H.; Wright, W. W., and Staffa, A. W.: Ant. Med. & Clin. Therapy 5:52 (Jan.) 1958. 3. Marlow, A. A., and Bartlett, G. R.: Glucosamine and Leukemia. Proc. Soc Exp. Biol. & Med. 84:41, 1953. 4. Shalowitz, M.: Clin. Rev. 1:25 (April) 1958. 5. Nathan, L. A.: Arch. Pediat. 75:251 (June) 1958. 6. Cornbleet, T.; Chesrow, E., and Barsky, S.: Ant. Med. & Clin. Therapy 5:328 (May) 1958. 7. Stone, M. L.; Sedlis, A. Bamford, J., and Bradley, W.: Ant. Med. & Clin. Therapy 5:322 (May) 1958. 8. Harris, H.: Clin. Rev. 1:15 (July) 1958.

The ultimate today in therapy for menopausal disorders, menstrual disorders, inoperable breast cancer, male climacteric.

A new oral androgen tablet with 5 times the potency of methyltestosterone tablets. Ultandren presents a new range of possibilities for simple, convenient treatment in conditions stemming from certain types of hormonal imbalance.

Small oral doses provide full androgenic effects, previously obtainable only with parenteral testosterone preparations. Easy tablet administration eliminates the painful injections, local reactions and skipped doses attending the use of intramuscular testosterone, as well as the foreboding aspects of treatment-room therapy. Begin now to prescribe Ultandren, truly the ultimate today in therapy for menopausal disorders, menstrual dysfunction and premenstrual tension, male climacteric, and palliation of inoperable SUPPLIED: ULTANDREN TABLETS, 2 mg. (light green,

ANNOUNCING two important new products



new PARAFON*

new PARAIFON* with PREDNISOLONE

now...the specific muscle relaxant

for relief of the pain-spasm-pain cycle

PARAF

(PARAFLEX Chlorzoxazone† plus Tylenol® Acetaminophen)

in arthritic and rheumatic disorders

PARAH with PREDNISO

McNEIL

McNEIL LABORATORIES, INC . PHILADELPHIA 32, PA.

plus the preferred analgesic



combines Paraflex, the effective low-dosage skeletal muscle relaxant that is specific for painful spasm, and Tylenol, the preferred analgesic for painful musculoskeletal disorders. Providing benefits that last for up to six hours, Parafon is effective on the practical dosage of only six tablets daily. Side effects are rare and seldom severe enough to warrant discontinuance of therapy. Parafon relieves pain and stiffness and helps improve function in acute and chronic low back disorders such as lumbago, acute paravertebral spasm, or sacroiliac strain; osteoarthritis; rheumatoid arthritis; traumatic hydrarthrosis; and traumatic muscle injuries.

supplied: Tablets, scored, pink, bottles of 50. Each tablet contains: Paraflex Chlorzoxazone 125 mg.; and Tylenol Acetaminophen 300 mg.

†U.S. Patent Pending *Trademark



adds the anti-inflammatory action of prednisolone to the relief of pain and spasm achieved with Parafon. Parafon with Prednisolone is useful in many arthritic and rheumatic disorders, such as rheumatoid arthritis, rheumatism, myositis, neuritis, tenosynovitis, fibrositis, bursitis, spondylitis, and osteoarthritis.

supplied: Tablets, scored, buff colored, bottles of 36. Each tablet contains: Paraflex Chlorzoxazone 125 mg., Tylenol Acetaminophen 300 mg., and prednisolone 1 mg.

announcing...oral iron under CHELATE control

exceptionally well tolerated the safest iron to have in the home



CHEL-IRON
BRAND OF IRON CHOLINE CITRATE®
TRADEMARK

CHELATED IRON

of the gastrointestinal tract, thus permitting an optimal physiological uptake ... ??



possesses outstanding qualities in terms of freedom from undesirable gastrointestinal effects.

The chelation of iron minimized its toxicity and provided a high factor of safety against fatal poisoning. ""

AVAILABLE AS: CHĒL-IRON TABLETS BOTTLES OF 100 3 tablets supply 120 mg. elemental iron. CHĒL-IRON PEDIATRIC DROPS 30-CC. BOTTLES with graduated dropper each cc. supplies 16 mg. elemental iron; 0.5 cc. provides full M.D.R. for infants and children up to six. CHĒL-IRON PLUS TABLETS BOTTLES OF 100 3 tablets supply 72 mg. elemental iron plus B_{12} with intrinsic factor, folic acid, pyridoxine, other essential B vitamins, and C.

*Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, Apr. 5, 1958. †U. S. Pat. 2,575,611



KINNEY & COMPANY, INC. COLUMBUS, INDIANA

Picture of a man getting bad advice about his dandruff



His friend means well, as friends always do. But his theories for the control of dandruff are constructed mostly from mail order advices, hints from his barber ... and intuition. The sad part of it is that neither one of them thinks to mention it to his doctor. They simply don't realize that dandruff—a medical problem—needs a medical answer. That's when a word from you, and a prescription for Selsun, will be most appreciated. Obbott

SELSUN®

(Selenium Sulfide, Abbott)

an ethical answer to a medical problem

2 IBEROL FILMTABS A DAY SUPPLY:

THE RIGHT AMOUNT OF IRON

PLUS THE COMPLETE B COMPLEX

 $\begin{array}{lll} \textbf{BEVIDORAL} & & & \textbf{1 U.S.P. Unit (Oral)} \\ \textbf{(Vitamin B}_{12} & \textbf{with Intrinsic Factor Concentrate, Abbott)} \end{array}$ Folic Acid...... 2 mg. Liver Fraction 2, N.F..... 200 mg. Thiamine Mononitrate 6 mg. Riboflavin..... 6 mg. Nicotinamide 30 mg. Pyridoxine Hydrochloride 3 mg. Calcium Pantothenate...... 6 mg. PLUS VITAMIN C

Ascorbic Acid 150 mg.

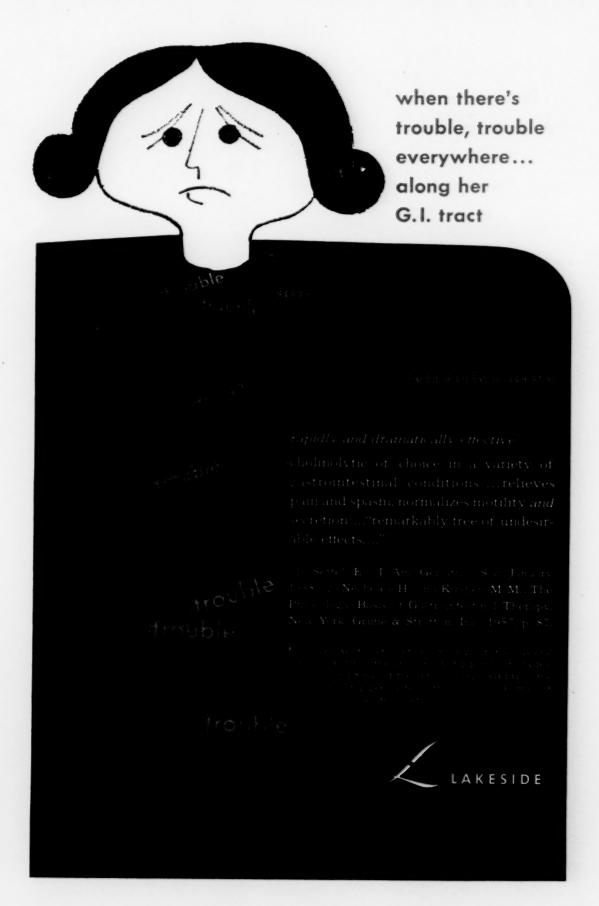
another indication for



potent antianemia therapy plus the complete B-complex abbott

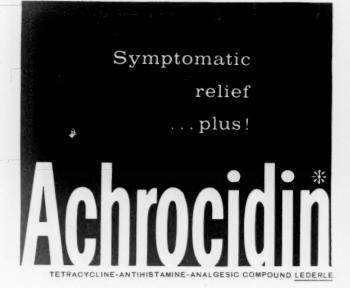
*Filmtab-Film-sealed tablets, Abbott; pat. applied for.

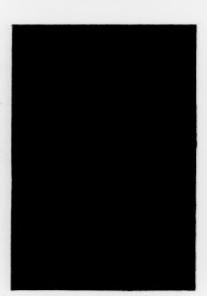












pneumonitis adenitis sinusitis otitis bronchitis

COMBINES: Traditional components for relief of the annoying symptoms of early upper respiratory infections . . .

PLUS: Protection against bacterial complica-tions often associated with such conditions.

TABLETS (sugar coated)

 TABLETS (sugar coated)

 Each contains:

 ACHROMYCIN* Tetracycline
 125 mg.

 Phenacetin
 120 mg.

 Caffeine
 30 mg.

 Salicylamide
 150 mg.

 Chlorothen Citrate
 25 mg.

 Bottles of 24 and 100.

SYRUP (lemon-lime flavored, caffeine-free)

 SYRUP (lemon-lime flavored, caffeine-free)

 Each 5 cc. teaspoonful contains:

 ACHROMYCIN* Tetracycline equivalent to Tetracycline HCl

 120 mg.

 Phenacetin
 120 mg.

 Salicylamide
 150 mg.

 Ascorbic Acid (C)
 25 mg.

 Pyrilamine Maleate
 15 mg.

 Methylparaben
 4 mg.

 Propylparaben
 1 mg.

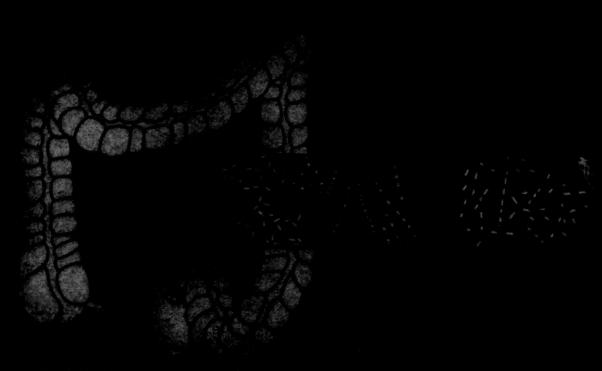
Bottle of 4 fl. oz.

Adult dosage for ACHROCIDIN Tablets and new caffeine-free Syrup is two tablets or tea-spoonfuls of syrup three or four times daily. Dosage for children adjusted according to age and weight.

Available on prescription only.



LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York *Reg. U. S. Pat. Off.



For more certain control of

virtually ALL DIARRHEAS

ANTIBIOTIC • ADSORBENT • DEMULCENT • ANTISPASMODIC

Diarripea the to nearly in susceptible pathogens are selfectively treated by the highly efficient intestinal antibotic in Doxyger with Neorygery, whose other ingredients serve to control toxic, institutes and emotional causes. Result Early resultable highly of normal boxel function.

SUPPLY Bottle of 6 th oz

ALSO AVAILABLE DONN LOTE the original formula to a cowhen the antibliotic component a not indicated. Bottle of oil of

Each 30 cc. (1 fl. oz.) of the comprehensive formula of DONNAGEL WITH NEOMYCIN contains:

Neomycin sulfate	0 mg.
Kaolin (90 gr.) 6.6	0 Gm.
Pectin (2 gr.) . 142.	8 mg.
Dihydroxyaluminum aminoacetate . 0.2	5 G m.
Hyoscyamine sulfate	mg.
Atropine sulfate 0.0194	1 mg.
Hyoscine hydrobromide 0.0065	5 mg.
Phenobarbital (% gr.) 16.2	2 mg.

HIGHLY EFFECTIVE ARTUST STAPHYLOCK AS CHLORUMYCETIN

Reports on studies of *in vitro* activity of CHLOROMYCETIN over the past few years indicate that this antibiotic has maintained its effectiveness against most strains of staphylococci. "... Staphylococci do not acquire resistance to chloramphenicol [CHLOROMYCETIN] as they do to other antibiotics, in spite of heavy use of chloramphenicol [CHLOROMYCETIN]."

These *in vitro* studies are borne out by excellent clinical results with CHLOROMYCETIN in treatment of patients for severe staphylococcal infections, including staphylococcal pneumonia,⁵ postoperative wound infections,⁶ postoperative parotitis,⁷ and puerperal breast abscesses.⁸

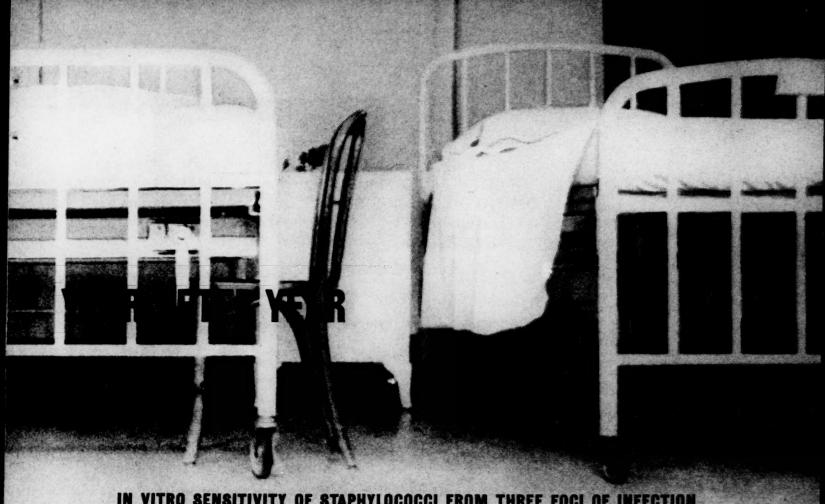
CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

REFERENCES: (1) Royer, A., in Welch, H., & Martí-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 783. (2) Waisbren, B. A., & Strelitzer, C. L.: Arch. Int. Med. 101:397, 1958. (3) Koch, R., & Donnell, G.: California Med. 87:313, 1957. (4) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: Canad. M. A. J. 77:844, 1957. (5) Cooper, M. L., & Keller, H. M.: J. Dis. Child. 95:245, 1958. (6) Caswell, H. T., et al.: Surg., Gynec. & Obst. 106:1, 1958. (7) Brown, J. V.; Sedwitz, J. L., & Hanner, J. M.: U. S. Armed Forces M. J.: 9:161, 1958. (8) Sarason, E. L., & Bauman, S.: Surg., Gynec. & Obst. 105:224, 1957.

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN





IN VITRO SENSITIVITY OF STAPHYLOCOCCI FROM THREE FOCI OF INFECTION TO CHLOROMYCETIN FROM 1953 TO 1957*

Skin (75 strains)		
		98.7%
Upper respiratory (84 strains):	86.9%	
(39 strains)	97	7.5%
OCTOBER, 1955-MARCH, 1956		
(113 strains)	4.	99.2%
Upper (137 strains)	97	1.8%
(45 strains)	97	1.8%
JUNE-DECEMBER. 1953		
kin (150 strains)	92.0%	
Upper (50 strains)	86.0%	
(70 strains)	90.0%	
0 20 40 60 80	100	0
*Adapted from Royer. ²	3125	a

new test for gastric acid now a simple office procedure

Diagnex Blue

Your patient swallows a liquid instead of a tube

- and the results are just as accurate.

- · eliminates discomfort and inconvenience of intubation
- · time-saving and economical; can be used in office
- · requires no special equipment
- · well-tolerated and completely safe

Diagnex Blue is easy to use:

- 1. The patient takes diagnex blue orally.
- 2. Urine samples are collected and returned to the physician.
- 3. Simple color comparison indicates gastric acid status.

Results are easily interpreted:

Free gastric acid is shown by color equal to or more intense than 0.6 mg. standard.

Absence of free gastric acid is shown by color equal to or less intense than the 0.3 mg. standard.

Borderline secretion is indicated by a color intermediate to these two standards.

 Diagnex Blue has been used in thousands of gastric analyses with conclusive evidence of accurate results (95% accurate identification of acid secretors, 97% accuracy in identifying achlorhydrics).

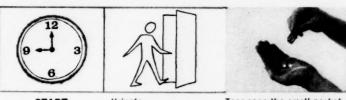
SQUIBB



Squibb Quality the Priceless Ingredient

how to perform the Diagnex Blue Test

This is what the physician tells the patient: Start test immediately on arising, without eating or drinking anything for breakfast.



START Urinate.

Do not keep this urine.

Tear open the small packet and swallow the 2 tablets with a glass of water.

marked "control urine". tents into 1/4 glass of water. granules do not dissolve.)



 $\begin{pmatrix} 12 \\ 0 \\ 6 \end{pmatrix}$

2 HRS. LATER

Urinate. Save urine in jar marked "test urine"

Test Procedure

Each box of DIAGNEX BLUE has a color comparator block with two color standards—one representing color intensity of 0.6 mg. azure A, and the other 0.3 mg. azure A. Color comparison should be made against a suitable light source.

- Dilute the control and test urines with water to 300 cc. each.
 - 2. Fill two test tubes with approximately 10 cc. of control urine each, and fill a third test tube with about 10 cc. of the test urine.
 - 3. Place the test urine tube in the middle slot of the comparator and the control urine tubes in front of the two color standards.
 - **4.** If the color intensity of the test urine is equal to or exceeds that of the 0.6 mg. standard, the patient has secreted free gastric hydrochloric acid and the test is complete.
- B. 1. If the test sample color is less intense in color

than the 0.6 mg. standard, acidify all samples with 2 drops of diluted (10%) hydrochloric acid. Heat the three test tubes in a boiling bath for 10 minutes. (Boiling may decolor sample, but color will reappear on cooling.) Remove tubes from the bath and allow to cool for 2 hours. Compare color intensity as in A3 and A4.

If granules remain, add a little more water and drink

them down.

2. When the color of the test specimen falls between the 0.6 mg. and the 0.3 mg. standards, this is presumptive evidence of hypochlorhydria. When the color of the test specimen is *less* intense than that of the 0.3 mg. standard, this is presumptive evidence of achlorhydria.

Supply: Boxes of 5 and 50 test units with comparators. Each test unit contains 2 Gm. DIAGNEX BLUE granules, two 250 mg. tablets of caffeine sodium benzoate to stimulate gastric secretion, and labels for urine samples. Complete instructions for use are included in each package.

Would ye	ou like
additional inform	nation
on diagnex	BLUE?

Simply mail this coupon.

Professional Service Department (11B)
SQUIBB, 745 Fifth Avenue, New York 22, N. Y.
Gentlemen: Please send a copy of your technical leaflet,
"A Tubeless Test for Gastric Acid" to:

Dr		
Address		

CYTELLIN REDUCES HYPERCHOLESTEREMIA Percentage reduction of excess serum cholesterol (over 150 mg. percent) Less than 20% 12.5% More than 40% 32.5%

... without the necessity of dietary restrictions

'Cytellin' provides the most rational and practical therapy available. Without any dietary adjustments, it lowers elevated serum cholesterol concentrations in most patients.

In a number of studies, every patient who co-operated obtained good results from 'Cytellin' therapy. On the average, a 34 percent reduction of excess serum cholesterol (over 150 mg. percent) has been experienced.

In addition to lowering hypercholesteremia, 'Cytellin' has been reported to effect reductions in C/Pratio, $S_f10-100$ and $S_f12-400$ lipoproteins, "atherogenic index," beta lipoproteins, and total lipids.

May we send more complete information and bibliography?

*'Cytellin' (Sitosterols, Lilly)

The American Journal of Medicine

Vol. XXV

NOVEMBER, 1958

No. 5

Introduction to a Symposium on Nutrition in Internal Medicine

THE justification for devoting a Symposium of the American Journal of Medicine to articles on nutrition, aside from the considerable value of the papers themselves, must be in the emphasis it gives to the importance of nutrition. That such emphasis may be needed or desirable is interesting and important, and in itself sufficient reason for such an action. That such a fundamental process as nutrition might need emphasis in medicine is likely to strike the layman or non-medical scientist as peculiar, to say the least. He is likely to reflect that in its various aspects nutrition is so important and so broad that it affects nearly every aspect of society. The history of nutrition is the history of life on this planet. It has been and is a tool of government, of politics, of war, and of conquest. It has affected exploration, discovery, colonization and the fate of populations. In modern life it involves agriculture, transportation, industry and trade, and with them all the socio-economic, scientific and cultural aspects of our society; all to the aim in the end, of the health and vigor of the individual human being, and the prevention, treatment and recovery from disease. How then can the importance of nutrition in medicine need

The story of nutrition as it relates to medicine is an uneven one. To the ancient Greeks it was a major factor in both causation and cure of disease. Down through the centuries it served both the honest physician and the quack, cultist and faddist, as it does today. Until the era of bacteriology and the understanding of infectious disease, it remained a major element in the theories of the cause of disease and, until the general

improvement in world economy in the present century, it was the actual cause of illness of millions, very often joining hands with infection to increase the ravages of each.

Actually, a combination of causes is responsible for the tendency to slight the importance of nutrition in modern medical practice, teaching, and to some extent, research. They are, not necessarily in the order of importance, the following:

The discovery, knowledge and prevention, relief and cure of infectious disease, especially by specific treatment. This not only limited to some extent interest in other disease, but, as specific treatment or prevention developed, it led to a neglect of the role of nutrition itself or as a complicating factor in infections. No physician experienced in the care of typhoid fever before prophylaxis, or before the days of successful drug treatment, could neglect the factor of nutrition, but how important is it considered today?

Coupled with the overriding interest in the more dramatic infectious diseases and in other better understood disease states, there was a lack of more detailed knowledge of the mechanisms of nutritional disease. With the exception of a few "metabolic" diseases such as diabetes, a knowledge of the pathogenesis of nutritional disease was confined largely to that of starvation (calorie deficiency) or obesity.

Nutrition was thus largely a matter of "nutritious food," of feeding and of attention to the grosser characteristics of the diet. Nutrition became dietetics, a valuable aspect of medical care and one which remains valuable today, but

one to be delegated to an auxiliary service and not a part of the particular armamentarium of the physician himself.

The discovery of the vitamins, their isolation and synthesis, caused a great upsurge of interest in nutrition. This, combined with an increasing knowledge of the role and behaviour of proteins, fats and minerals, greatly expanded our knowledge, and with it, our interest in nutrition. To this must be added the dramatic and unexpected appearance of widespread starvation and nutritional disease in the western countries as a result of the first World War (to some extent the same occurred in certain parts of the world in World War II). Paradoxically, however, this same great advance in our knowledge of nutrition (vitamins, protein, fat and minerals) led to a decreased interest among physicians generally. This is not hard to understand.

To begin with, this new knowledge became available at a time when the economic situation in the United States, Western Europe, and indeed, to some extent, throughout the world, was improving at a remarkable rate and to an unprecedented level. Even in underdeveloped parts of the world, part of this economic gain was translated into some modest improvement in nutritional health, largely through the efforts of the Technical Commission on Nutrition of the League of Nations. Even World War II, which interfered severely with economic improvement, paradoxically resulted in the improved nutrition of many populations by virtue of rationing and governmental control of food supplies which resulted in a more even distribution. (In England the availability of milk was greatly increased and many, many more people had a fair allowance, while the previously larger amount obtained by the few was reduced.) Even in Germany and her satellites rationing and government-controlled collection and distribution of food resulted in an improved level of food consumption and nutrition more generally distributed, until the late stages of the war when the system as well as supplies broke down. In this country, in Canada, and to some extent in other countries, the enrichment (vitamin and mineral) of certain basic foods and the education of the public in the choice and selection of food by many agencies aided in improving nutrition. Finally, to this must be added, particularly in the United States, the dubious effect of rather widespread consumption of artificial

(pharmaceutical) forms of vitamins and other nutrients, with and without the recommendation of physicians and with the benevolent suggestion and urging of pharmaceutical and chemical manufacturers.

All this was based on our new knowledge of nutrition. The result was virtual disappearance of the previously well known and classic diseases or syndromes of nutritional deficiency, pellagra, scurvy, beriberi, xerophthalmia, night blindness, rickets, and newly discovered diseases such as riboflavin deficiency, except for occasional sporadic instances of conditioned nutritional disease such as alcoholic pellagra. There remained, of course, an unknown but debatable amount of deficiency disease below the level of gross, easily detectable illness, such as pellagra and scurvy. Controversy at once developed as to the amount of such "subclinical" deficiency disease, the drug manufacturers and nutrition enthusiasts, some doctors, but more often laymen, holding out for a vast amount of such illness-most doctors, failing, according to their experience, to find it, decrying such estimates.

However, the principal effect of all of this on the doctor was to lessen his interest in the medical aspects of nutrition and particularly in the more basic aspects of etiology, pathogenesis, the diagnostic procedures needed to detect mild or complicated deficiency disease, or the detailed care necessary to secure the maximum results of treatment. Unfortunately, the treatment of much of such disease is specific, easy, and almost without danger. If nutritional deficiency was suspected or anticipated, in particular early or mild forms, it was easy and popular to prescribe vitamin and mineral pills or capsules. If in doubt as to the exact kind of deficiency present, a combination of several vitamins and/or minerals could be prescribed. Only in the case of caloric or protein deficiency, often accompanied by feeding problems, did difficulties appear to arise.

The final and perhaps the greatest factor contributing to neglect of nutrition is, curiously, the body's reserve and its margin of safety. Unfortunately perhaps, the human organism (and most other animals') is able to function at a minimal or subminimal level of nutrition without it becoming apparent. In other words, we do not know the optimum of nutrition, or, from a practical and practicing viewpoint, a better nutrition beyond the rather gross limits. In medical practice, we often make no effort, or an insufficient

effort, to obtain the maximum benefits of nutrition as a factor in the prevention, relief or cure of disease. The same might be said with respect to the nutrition of populations (public health nutrition), although this presents certain other aspects not to be discussed at present. Such neglect, however, is more than disinterest; actually, it is the great difficulty in medical practice of securing the best possible nutrition as we know it. The many factors of nursing, dietetics, patient cooperation, laboratory facilities, hospitalization and others present problems which are often beyond the resources of even a conscientious and capable physician. Let me illustrate by comparison with another type of problem: A good mortality rate in the operative treatment of exophthalmic goiter is, let us say for this purpose, 1 per cent. By careful selection of patients, meticulous pre- and postoperative preparation and care, and the judicious use of all auxiliary aids it can perhaps be reduced to 0.5 per cent. Such an improvement is difficult and costly, and with each succeeding degree of improvement the difficulty and cost increase in ascending degree. Similarly, if one is to obtain the maximum results from the use of our present knowledge of nutrition, which is present as a modifying or complicating factor in nearly every illness or disease state, one must indeed put forth a great effort.

Such efforts should be made and increasing

attention must be paid to the medical aspect of nutrition. In the field of research, nutrition may hold the key to the nature and control of neoplastic diseases. It will have a role in relation to radiation injury. It offers unexplored potentials in relation to other disease, ranging from congential deformities to the degenerative diseases. The latter in particular bring to our attention an aspect of nutrition often overlooked and largely unknown, for want of a better word, "overnutrition." Obesity is, of course, well known and the subject of increasing attention. There may be other forms, however, less well known or indeed, unknown, which wait to confront us in the future. The good effects of "better" nutrition are well known. The decrease and disappearance of pellagra, beriberi and scurvy are highly beneficial. But what lies beyond? The beneficial effects of improved nutrition in the way of larger, more rapidly growing children and young adults (as well as the survival of perhaps inferior persons) are clearly apparent. But does this "improvement" carry with it the germ of later disaster, i.e., earlier degenerative disease? This is an example of the many interesting and important aspects of nutrition which await study and understanding, that emphasize the ever increasing importance of nutrition in medicine.

> John B. Youmans, M.D. Vanderbilt University School of Medicine Nashville, Tennessee

Symposium on Nutrition in Internal Medicine

Nutrition in Internal Medicine*

R. H. KAMPMEIER, M.D.

Nashville, Tennessee

In the distant past nutrition was interpreted in essence colol. in essence, solely in terms of caloric intake, whether adequate, inadequate or in excess, as related to weight. Although it was known two centuries ago that the clinical syndromes of beriberi and scurvy responded to some substance included in food, and others of the deficiency diseases had been described, it was not until 1913 that the entity of vitamin A deficiency was established. The essential need for other vitamins was then rapidly recognized, and knowledge of deficiency states or disease entities quickly advanced. Thus was ushered in the era of the vitamin diseases, an era not yet closed since the demonstration of new vitamins and their need continues apace. Knowledge of the specificity of the amino acids and of fatty acids as essential elements in the synthesis of tissues has broadened concepts of the role of proteins and fats in nutrition. And, finally, there is an expanding appreciation that minerals are essential to the living processes of the cell and organism, iron, iodine, potassium, sodium, and those minerals which appear in trace amounts but in some instances play essential roles in the metabolic processes of the cell.

In the presumed metabolic equilibrium which determines health, the essential elements of nutrition must be presented to the tissues in such amounts that the metabolic needs of the cells may be met. Insufficient amounts of these essentials, whether in intake or because of malabsorption or of circumstances interfering with their utilization by the cell, or because of a heightened need, threaten disease. An excess of certain elements also may lead to abnormalities in the metabolic processes, and thus again constitute disease. Yet it is not as simple as this, for

all too commonly the factors related to these abnormalities are so complex that the interrelationships are not clear. The disturbances in caloric intake, whether due to excess with resultant obesity or to an inadequate intake as in starvation, are obvious. But, in addition, there are less clear-cut nutritional disturbances related to almost all diseases of interest to the internist, either as cause or effect. Not uncommonly these disturbances may be multiple and thus there may be a number of simultaneous causes and effects.

The appetite of the normal adult usually keeps pace with metabolic needs, and the weight shows little fluctuation. But appetite sometimes remains a fixed variable although need is lessened, as is well demonstrated upon the adult's entry into middle age, at a time when physical activity may be decreased and hormonal alterations may play a part, but appetite may continue at its previous level, with increasing weight. Not infrequently obesity stems from a habit of excessive eating, a familial characteristic of the family which sets a "good table." And then there is that excess of eating, a psychiatric equivalent to alcoholism, a substitute in satisfying an emotional need. Decreased metabolic needs reflected in weight gain is, of course, well shown in hypothyroidism. (Only rarely is a pathologic appetite a symptom of organic disease, as in disease of the hypothalamic region.)

Obesity, then, is a common problem for the internist, especially in his management of the middle-aged patient. This is a problem to be faced because herein lies possibly the major consideration in preventive medicine in this country, now that infectious diseases have be-

^{*} From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.

come a minor hazard. The association with obesity of diabetes mellitus, arteriosclerosis, osteoarthritis, and of hypertension with resultant heart disease makes the control of obesity a daily responsibility of the practicing internist in the prevention of disease and in extending the patient's life into healthful years.

The effects of obesity upon the cardiovascular system are specific, and since the most common cause of death in our population lies in the sphere of cardiac disease, it deserves particular emphasis. Not only does obesity require increased work of the aging myocardium as the individual transports pounds of inert tissue from place to place, but the increased blood volume required to provide the oxygen and nutrients to this mass of tissue presents to the heart a load of work which should and can be avoided. Added to the load of work may be the common accompaniment of arteriosclerosis which, if of the coronary arteries, reduces the effective blood flow to the myocardium. If all these burdens placed on the circulation are not enough of a handicap, one may add still another factor the magnitude of which possibly has not vet been fully appreciated. Only recently have studies of pulmonary function clearly shown that increased intra-abdominal pressure or increase in girth is accompanied by a decrease in expiratory reserve, and that in the extreme instance there may actually be a relative ventilatory insufficiency. Although "obesity heart disease" manifested as failure of the right chamber may be the rare end-manifestation of such an exaggerated state, one may ask, have the effects of decreased expiratory reserve been evaluated as a factor in myocardial efficiency in the obese middle-aged person? The salutary effect of reduction of weight upon hypertension has been recognized for decades. Whether this is dependent alone upon a reduction in blood volume or a decrease in vascular bed is not known. In any event, the effect of a reduction in hypertension upon cardiovascular disease needs no emphasis.

That diabetes mellitus beyond the earlier decades of life is associated in some way with obesity is proved by the high coincidence of these two states and the frequent ease of control of the diabetic state by weight reduction, even though the hypotheses attempting to explain the association are not entirely satisfactory.

The clinical manifestations of degenerative arthritis, commonly ameliorated by weight reduction, demonstrate the effect of excess weight upon the joints which over the years have shown the effects of "stress and strain."

Although obesity is obvious and its effects quite readily understood, pointing the way to prophylactic or to symptomatic treatment, weight loss and undernutrition not uncommonly raise diagnostic problems. If the history does not reveal voluntary "dietary" fads in eating, or inability to buy sufficient food, the physician can not rest his case until every effort has been made to explain the loss of weight. The psychiatric states of depressive reaction or of anorexia nervosa account for undernutrition in some instances. Loss of weight through a heightened metabolic rate, as in fever or in thyrotoxicosis, and through loss by glycosuria in the diabetic is common enough. The lessened intake of calories or their loss by vomiting or diarrhea because of malignancy of the gastrointestinal tract also occurs commonly. Abnormalities of the absorptive mechanisms, because of pancreatitis or disease of the lower bowel, may offer an explanation for a puzzling state of undernutrition, although such causes at times are hidden, particularly if anticipated symptoms have been controlled by medication or voluntary dietary restrictions. In this area lies the particular need of careful and analytic history taking.

Undernutrition, of whatever cause, must be given attention, either in a search for its cause and its correction, or in an effort to supply the needed calories by whatever means and modifications of diet that may be necessary. Such dietary means must include also consideration of the adequacy of the diet in factors other than calories, for not only is this undernutrition, but practically always malnutrition as well, expressed as an inadequacy of essential dietary factors.

Even though undernutrition may not be apparent, in terms of calories or weight loss, malnutrition may be reflected in an inadequacy of essential factors which can not be synthesized within the body. Such deficiency states may not be recognized in an early state unless they are kept in mind in taking a dietary history.

The normal person, unless a food faddist, almost always ingests quantities of protein sufficient to insure an adequate supply of the essential amino acids and to remain in positive nitrogen balance. One may, to be sure, encounter instances of protein deficiency in those who have poor dietary habits or are unable to

buy protein foods, and in women who have had excessive demands upon available proteins during pregnancy and lactation. But protein deficiency must be suspected and searched for particularly in those who, through poor judgment, have been advised to use low protein diets, or in those who have lost blood through bleeding and have had a diet insufficient in protein. Commonly, protein deficiency represents only one phase of malnutrition or malabsorption in diseases of the gastrointestinal tract. One need hardly comment upon the loss of protein in the proteinuria of renal disease.

More specifically, one must keep in mind deficiencies in certain essential amino acids which the body can not synthesize, at least at the required rate. Such a deficiency in certain amino acids may develop because of increased need, or abnormal metabolism in specific diseases, as in chronic hepatic and renal diseases and in thyrotoxicosis. Thus protein deficiency and, more specifically, deficiency of essential amino acids constitute phases of nutrition not infrequently overlooked, and to be considered particularly in the chronically ill patient. The symptoms of weakness resulting from such deficiencies may be thought to be related to vitamin deficiency and indeed, in view of the metabolic relationships between certain essential amino acids and members of the B-complex, their interrelationship in respect to symptoms possibly cannot be denied. Dietary management should include recognition of these facts.

There is accumulating evidence that fat may represent not merely a source of energy but that certain fatty acids cannot be synthesized by the body and are essential for specific metabolic processes. This phase of nutrition, based on observations in infants kept on a fat-free diet, needs

further study and clarification.

Deficiencies in vitamins usually are anticipated as an accompaniment of undernutrition or malnutrition, but one should be equally aware of the possibility of a vitamin deficient state in the presence of calorically adequate nutrition. Vitamins are essential components of enzyme systems involved in various metabolic processes in the body, and their presence in the body is dependent upon the diet since they cannot be synthesized by the human organism, although in some instances such synthesis can occur by the action of intestinal bacteria upon vitaminprecursors in the diet. Fortunately, the essential vitamins are stored in the body for many months,

protection against the variable ingestion of vitamin-rich foods. Fortunate also, is the ease of absorption of the water-soluble vitamins of ascorbic acid and of the B-complex, with the exception of B₁₂. On the other hand, diseases of malabsorption in the gastrointestinal tract and of biliary obstruction have an unfavorable influence on the absorption of the fat-soluble vitamins A, D, E, K, and of carotene. The watersoluble vitamins may be excreted in excess in the urine, so there are no toxic effects after excessive intake. However, this is not true of the fatsoluble vitamins, and excessive intake, particularly of vitamin D, may be extremely toxic and lead to serious disturbances in the metabolism of calcium and phosphorus.

The "vitamin era" has not drawn to a close. Not infrequently the role of a vitamin or the effect of its absence has been clearly established in the experimental animal, but many years may pass before its place in human metabolism can be established. Thus we may anticipate at some future date such data relative to vitamin E and to pantothenic acid. Only recently has the place of pyridoxine (B6) been fixed in the body economy and the relative deficiency which accompanies antituberculosis therapy with INH

been shown.

The role of folic acid in deficiency states has not been completely established. That it has a place in hematopoiesis (deficiency resulting in a macrocytic anemia) and in normal intestinal absorption is without question, but certain other possible effects have not been clarified. For example, it has been known to reverse glossitis unassociated with symptoms usually thought to be characteristic of sprue, and in persons with no evidence of anemia.

Another interesting phase of vitamins in nutrition concerns the antivitamins or vitamin antagonists, substances which compete with vitamins in enzyme systems, destroy them, or bind them so that they are ineffective. There is growing knowledge of these effects, which may be of far-reaching influence on the body economy. It is well, too, for the physician to recognize that drugs may compete with vitamins in metabolic processes, and that they may interfere with and, by alteration of the intestinal bacterial flora, prevent or reduce the synthesis of essential substances in the gut. This may be akin to what has been shown to occur in plant life, where it has been demonstrated that "toxic products" of infectious agents may block enzyme

systems within the cell. Here is a facet of "nutrition" not yet explored in man—"nutrition" in terms of interference with cellular metabolism.

Although the full-blown syndromes of vitamin deficiencies are well known and quite readily recognized, one should bear in mind the earliest changes which may herald what might develop into a clear-cut clinical picture. Actually, one wonders what part subclinical impairment of enzyme systems may play in chronic disease. Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon tissues in chronic disease. Are there "subclinical" degrees of vitamin deficiencies to search for, now that frank deficiency states have become so rare at least in the United States?

The minerals playing a role in the body economy are also to be considered in the nutritional aspects of health. The importance of sodium, potassium, calcium, phosphorus, iron and iodine is appreciated. Although there is less positive information regarding many of the trace metals, their place in metabolic processes in some instances has been finally established. The need for iron in the prevention of iron deficiency anemia with, at times, attendant symptoms of the Plummer-Vinson syndrome, is common knowledge. Other than iron deficiency on the basis of intake in early childhood, deficiency of iron occurs usually with inadequate replacement of losses by bleeding; in women in the lower economic levels, with a rapid succession of pregnancies and/or menorrhagia the diet may be inadequate to replace iron lost. There are also the mild anemias of the iron deficiency type, hardly recognized, in chronic disease. Who can say whether the minimal or relative anoxia of a mere reduction of 2 gm. per cent of hemoglobin has a deleterious effect upon a myocardium already damaged, or in the metabolic processes of tissues already impaired by chronic disease? There is reason to believe that such subclinical

anemias or anoxia play a part in chronic disease and in its response to therapy.

The nutritional and metabolic interrelationship of calcium, phosphorus, parathormone and vitamin D are well known, as are the effects of their provision in excess or in insufficient quantity. The place of iodine in the body economy was established long ago, and is well understood in its clinical implications as related to the thyroid hormone. Its deficiency especially presented a nutritional problem in the past, because of colloid goiter, and this still is an important problem in preventive medicine in certain areas of the world, not only in the adult but in the offspring as well. The role of cobalt in the enzyme systems of hematopoiesis was revealed only with the isolation of vitamin B₁₂. The part fluorine plays in dental health is recent knowledge; whether or not this element has other roles is not known. Recent studies indicate that magnesium and copper have active parts in the metabolism of certain tissues. The roles of zinc and cadmium are still in the shadows, but they probably will be on the clinical stage at some future time.

The science of nutrition has moved a long way in only half a century, from a consideration only of calories and the energy supplied by them to the intricacies of cellular metabolism. It has moved into the recognition of life processes through the roles played by the essential nutritive factors as catalysts of the enzyme systems needed for cellular activity. There is reason to believe that subclinical degrees of deficient nutrients influence the cellular activities in both health and disease. By an awareness of this, as well as of the more definitive deficiencies, the clinician can play an important role in preventive medicine. In retrospect, many errors have been made in the therapeutic diets of the pastdiets for peptic ulcer, renal, cardiac and hepatic disease-errors of ignorance. In the future the physician should inquire into more subtle errors, unbalancing of the delicate enzymatic reactions by alterations in electrolyte balance, which may shift essential ions, or by the use of drugs that compete with cellular enzyme systems. Here are aspects of nutrition that have not been viewed too critically and surely deserve our attention.

The Physiologic Role of Vitamins*

WENDELL H. GRIFFITH, PH.D.

Los Angeles, California

THE simplest classification of nutrients in foodstuffs depends on whether the primary use of the nutrient in the body is for the provision of energy or for the building of structural tissues. If one's concept of structural elements is in terms of bone and connective tissue with exclusion of particulate matter in the cytoplasm of cells, then the vitamins belong in neither of these two categories. For our purpose today vitamins may be considered provisionally as dietary essentials required with hormones and other products of endogenous origin in the maintenance of the complex equilibria which together make possible a steady state in the organism, a state not of rigid constancy but one quickly adjustable to normal and abnormal stresses.

The diversity of the molecular structure of vitamins is striking and it is clear that their function is not dependent on any one common structural configuration or chemical property. Hormones also show such individual variations. However, hormones differ from vitamins in at least two respects. They are not dietary essentials and several have protein structures. Significantly, there is no known instance of a specific protein that is indispensable in the dietary.

Whether or not other essential nutrients such as trace minerals, essential amino acids and essential fatty acids should be classed with the vitamin group is largely a matter of arbitrary definition. If desired, trace minerals can be excluded by explicitly describing vitamins as organic compounds. Similarly, essential amino acids can be put in the category of tissue building materials. The unsaturated fatty acid, arachidonic acid, is more of a problem and might easily qualify as a vitamin unless it also is found to function largely in the form of phospholipides or other derivatives used in cell walls and in brain and nerve tissue. However, no advantage is to be gained in the broadening or narrowing of definitions in order to achieve an unnatural or unrealistic pattern of conformity in the classification of nutrients, and this will not be attempted.

A discussion of the physiologic role of the vitamins at this time can only be in the nature of an interim report. Despite the detailed information which has accumulated during this last half-century we are now possibly no more than at the beginning of an understanding of these bewildering constituents of food. True, rather precise statements can be made concerning the mechanism of transport of hydrogen atoms by certain riboflavin-containing protein complexes but this gain is matched by our inability to name any chemical reactions through which another vitamin, the antirachitic vitamin, has been proved to facilitate the utilization of food calcium for the formation of bone. True, the role of vitamin A in vision has been nicely delineated but there is a complete lack of recognition of the manner of its beneficent protection of epithelial cells, whether of the eye, the skin, the gastrointestinal tract or the reproductive tract. Research has linked thiamine, nicotinamide and pantothenic acid with the utilization of the carbons of pyruvic acid in the highly important citric acid cycle in animal tissues; vet, in man, beriberi results from a deficiency of thiamine, pellagra from a deficiency of nicotinamide, and no comparable deficiency disease has been associated with pantothenic acid. Although the latter statement possibly is an oversimplification of the situation one may well ask if the facts at hand, as astonishing and as useful as they are, represent only the more easily recognized aspects of the activity of certain of the vitamins.

Be that as it may, the fact is that a well characterized, acute syndrome in man, beriberi, can be prevented by the daily addition of approximately 1 mg. of pure thiamine to a thiamine-deficient diet. Similarly, each of the other historically important nutritional deficiency diseases, pellagra, scurvy, xerophthalmia and rickets, can be prevented by the daily addition of appropriate amounts of pure niacinamide, ascorbic acid, vitamin A and vitamin D₂ (or D₃), respectively, to the corresponding deficient

^{*} From the Department of Physiological Chemistry, University of California Medical Center, Los Angeles 24, California.

dietary. Furthermore, the observations that have related certain vitamins to physiologic mechanisms, if not to the disease processes themselves, demonstrate convincingly that participation in catalysis as a part of intracellular enzyme systems is one function, at least, of a number of the vitamins Thiamine has been so implicated from the very beginning, first by thoughtful hypothesis and later by a fascinating series of experimental observations. The development of the concept which ascribed a catalytic function to thiamine thus parallels the record of its recognition and subsequent study.

In 1913, two years after the publication of the epochal report which described the experiments that demonstrated unequivocally the existence of accessory food factors, F. Gowland Hopkins made an equally momentous address before the Physiological Section of the British Association for the Advancement of Science [7]. His remarks were especially noteworthy because of the skill and awareness with which he portrayed the knowns in the metabolism of animals and because of the persuasiveness of his appeal to organic chemists to investigate the unknowns in the living processes in animals. To him, vital phenomena represented an unfolding and exciting organization of interdependent chemical reactions, a truly dynamic state. In decrying the widespread tendency of chemists to consider metabolic reactions virtually impossible to study and to comprehend because of the assumed involvement of only enormously complex and more or less static molecules, and to content themselves therefore with the proximate analysis of non-living tissues, Professor Hopkins spoke as follows:

"But the last fifteen years have seen grow up a doctrine of a quite different sort which, while it has difficulties of its own, has the supreme merit of possessing an experimental basis and of encouraging by its very nature further experimental work. I mean the conception that each chemical reaction within the cell is directed and controlled by a specific catalyst. I have already more than once implicitly assumed the existence of intracellular enzymes."

The significance of this statement becomes apparent as one reads his 1911 paper on accessory dietary factors [2], for here he writes:

"It is possible that what is absent from artificial diets and supplied in such addenda as milk and tissue extracts is of the nature of an organic complex (or of complexes) which the body can-

not synthesize. But the amount which seems sufficient to secure growth is so small that a catalytic or stimulating function seems more likely. It is probable that our conception of stimulating substances, 'Reizstoffe,' may have to be extended. . . . Stimulation of the internal secretions of the thyroid and pituitary glands, which are believed, on very suggestive evidence, to play an important part in growth processes, can be legitimately thought of. On the other hand, the influence upon growing tissues may be direct. If the attachment of such indispensable functions to specific accessory constituents of diets is foreign to current views upon nutrition, so also is the experimental fact that young animals may fail to grow when they are daily absorbing a sufficiency of formative material and energy for the purposes of growth."

These were prophetic words indeed, and at the time entirely without experimental verification. Only fourteen years had passed since Buchner had shown that "formed" ferments of the intact yeast cell were also active as "unformed" ferments in cell-free systems, the "enzymes" of Kühne; fifteen more years were to pass before Sumner was to isolate the first crystalline enzyme, the simple protein, urease; and twenty-six years were to pass before Lohmann and Schuster [3] were to demonstrate that the enzyme carboxylase is a conjugated protein with thiamine pyrophosphate as its coenzyme or

prosthetic group.

It is obvious that Hopkins visualized the probability that the newly recognized nutrients, named "vitamines" by Funk in 1912, would play important roles in metabolic reactions. Experience and experiment for over one hundred and fifty years had been providing mankind with apparently irresistible, but nevertheless neglected, evidence of the existence in foodstuffs of indispensable substances other than protein, fat, carbohydrate and minerals. For example, observations of the beneficial effect of fresh vegetables and fruits in the treatment of scurvy were generally disregarded until the demonstration of the curative action of citrus fruit juice in scorbutic sailors in a controlled experiment by Dr. James Lind in 1757. Significantly Lind's findings resulted in official regulations for the issue of lime juice to sailors of the British Navy and Merchant Marine, but not until 1804 and 1866, respectively.

Dumas in 1871 wrote convincingly of the tragic consequences of the attempt to nourish infants on artificial milk during the siege of Paris [4]. Ten years later Lunin, working in von Bunge's laboratory on the subject of inorganic salts in diets, noted that mice could subsist on milk for at least sixty days but quickly succumbed on a mixture of casein, lactose, milk fat and milk ash. His conclusion that other food essentials than these materials are present in milk was abundantly verified by Hopkins' data,

published some thirty years later.

The virtual disappearance of beriberi in the Japanese Navy following the substitution of barley and meat for part of the rice under Takaki's supervision in 1885 might well have paved the way for an early solution of the beriberi enigma. Unhappily, Eïjkman, whose recognition and experimental application of avian polyneuritis made possible the subsequent irrefutable proof by Funk of the existence of an antineuritic or antiberiberi substance, spent years proving that the effectiveness of the protective substance in the outer coating of the rice kernel was not due to its neutralization of pathogenic organisms or of a specific toxin in white or polished rice. Hopkins in commenting on this recurring difficulty in accepting the concept of a missing factor wrote [5]:

"The whole trend of modern pathology had made our minds ill prepared to believe in an extraneous deficiency as a cause of disease . . . the essential and immediate cause of any disease we rather seek in the intrusion of some positive factor, some *res noxia*, be it parasite or

poison."

The culmination of these studies, insofar as the vitamin thiamine is concerned, came in 1911 with Funk's publication of his experiments on the attempted isolation of an antiberiberi compound from rice bran [6]. Crystalline material was obtained which cured polyneuritic pigeons when administered in doses of 20 to 40 mg. This report about the new "organic base," now known to have been a relatively impure mixture, served as a spark, nevertheless, which almost explosively changed the course of experimentation in nutrition. The studies of Funk received immediate support in a most surprising fashion, for during the next two years came the reports by Hopkins on accessory growth factors for rats in milk [2], by Holst and Frölich on the dietary prevention of scurvy in guinea pigs [7], and by Osborne and Mendel [8], and by McCollum and Davis [9] on the presence of antixerophthalmic factors in fats such as butter fat and cod liver oil. Thirteen

years were to pass before pure crystals of thiamine were obtained by Jansen and Donath [10], and twenty-three years before the structure of the thiamine molecule was known and synthesis became a reality [11], but lack of crystalline products and absence of identity proved no bar to the rapid expansion of research on the vitamin content of foods and on the physiologic role of the vitamins.

Confirmation of the enzymatic and catalytic nature of the antiberiberi activity of the vitamin resulted from the extensive investigations of Peters and his co-workers. Peters reviewed the earlier studies in a paper published in 1936 and appropriately entitled, "The Biochemical Lesion in Vitamin B₁ Deficiency" [12]. With an initial objective of finding a more satisfactory and convenient test for the vitamin than the prevention of opisthotonos and related signs of avitaminosis in the pigeon fed polished rice. Peters turned to the chemical study of pigeon brain. Carefully performed analyses showed a higher concentration of lactic acid in the brain tissue from deficient birds. Utilizing the new technics for measurement of respiration in tissue slices and minces developed by Warburg and by Dickens and others, Peters noted that minced brain tissue from thiamine-deficient pigeons used oxygen at a slower rate in the presence of glucose as an added substrate than did tissue from normal birds. One can imagine the interest with which the key experiment was then performed, viz., the determination of the effect of additions of small amounts of the purified antineuritic vitamin on the lessened rate of oxygen uptake of the deficient brain tissues. The rate was accelerated and Peters became the first to show that one member, at least, of this new class of nutrients exhibited an in vitro biological activity. The possibility that the accelerated respiration of deficient brain tissue in the presence of added thiamine in the Warburg flask might be identical with the change taking place in the brain and other tissues following administration of the vitamin to deficient pigeons intensified the significance of these important findings. This effect of thiamine in removing the biochemical lesion in thiamine avitaminosis, called by Peters the catatorulin test or reaction, was considered catalysis because of the minute amount required. In a system containing 100 mg. of minced brain, wet weight, in 3 ml. of Ringer's phosphate medium the effect of as little as 0.0001 mg. of the vitamin was

measurable. Furthermore, a maximal effect was exerted by 0.05 mg.

The catatorulin test proved useful as a measure of thiamine deficiency in pigeons but it was much more important as a laboratory tool in the study of the physiological mechanism of thiamine activity. Peters had assumed up to this time that thiamine was needed for the oxidative removal of lactic acid formed by the glycolysis of glucose. Interestingly, it had no effect on the oxidation of succinic acid. Its influence, therefore, appeared directly concerned with the 3-carbon intermediates formed during anaerobic glycolysis of glucose. As Peters has commented, he was shocked to find that lactic acid was not decreased during the in vitro respiration of brain tissue from thiamine-deficient birds in the presence of added thiamine. During this period both Embden and Meyerhof were demonstrating independently the importance of pyruvic acid in intermediary carbohydrate metabolism. Repeating the catatorulin test with analyses for pyruvic acid, Peters was able to show that this acid was not present in appreciable amounts in respiring brain tissue of normal pigeons, that it was formed from lactic acid in deficient brain tissue but not if thiamine was added, that added pyruvic acid disappeared in the presence of thiamine, and that its disappearance was proportional to the uptake of oxygen. These experiments were the basis of subsequent studies which demonstrated elevated levels of pyruvic acid in the blood of human patients with beriberi.

As early as 1911 Neuberg and Karczag had reported an enzyme, carboxylase, in yeast which was involved in the conversion of ethanol to pyruvic acid and carbon dioxide [13]. Later, Auhagen reported the occurrence of carboxylase in animal tissues as well as in yeast and noted that the activity in yeast disappeared after washing with alkaline phosphate solution [14]. He concluded that carboxylase contained a coenzyme which was easily removable. In 1937 Lohmann and Schuster isolated the coenzyme from yeast and demonstrated that it was the pyrophosphate of thiamine [3].

It was quickly shown that thiamine pyrophosphate, or cocarboxylase, is the form in which thiamine is largely found in animal tissues; that it is, in fact, decreased in thiamine-deficient animals and that it is increased in these tissues following administration of thiamine. Lohmann and Schuster reported that cocarboxylase was as effective as thiamine in the curing of poly-

neuritic birds and in the catatorulin test. It is an interesting side light on these experiments that Peters was unable to confirm the observations of Lohmann and Schuster except as he employed a much finer dispersion of brain tissue than he customarily used in the test. The apparent discrepancy was solved when it was shown that thiamine pyrophosphate did not easily diffuse into the tissue. It was also shown that in the catatorulin test, in which thiamine exerted its in vitro activity, the effect was dependent on the diffusion of the vitamin into the cell and its phosphorylation in the cell to the active compound, thiamine pyrophosphate.

The decarboxylation of pyruvic acid with the formation of carbon dioxide and of a 2-carbon component is a primary reaction in glucose metabolism in animals and in alcoholic fermentation in yeast and in the metabolism of pyruvate in various microorganisms. In every instance thiamine pyrophosphate is an obligatory coenzyme. In addition, cocarboxylase is required in the conversion of alpha-ketoglutaric acid to succinic acid.

Thus, the normal working of the citric acid or tricarboxylic acid cycle requires the presence of the phosphorylated vitamin at two points, in the reaction by which acetate from pyruvate enters the cycle and in the reaction which results in the formation of succinic acid. The decarboxylations of the two alpha-keto acids apparently have the same requirements, viz., carboxylase with thiamine pyrophosphate as the coenzyme, magnesium ions, oxidized diphosphopyridine nucleotide (DPN+), lipoic acid and coenzyme A. It is a pertinent indication of the importance of vitamins to find that this one reaction in which carbon dioxide is split out from pyruvic acid and which starts the other two carbons on their way to final oxidation to carbon dioxide not only requires thiamine as a participant but also two additional vitamins, nicotinamide as a constituent of DPN and pantothenic acid as a constituent of coenzyme A. Furthermore, these reactions in which decarboxylation occurs would not be carried to completion if still another vitamin, riboflavin, were not available as a hydrogen acceptor and carrier. What is the physiological role of the vitamins? The answer is obvious in so far as these vitamins are concerned. They play essential parts in the acceleration of the most basic energy-transferring reactions of both plants and animals.

Although acceptance of the catalysis of

metabolic reactions as a physiologic function of vitamins is justified it is important to recognize clearly the limitations of such a conclusion. Enzymes are the agents which in trace amounts in the body accelerate specific chemical reactions without necessarily affecting the equilibrium constants of reversible systems or being used up in the process. It is the enzymes that make it possible for metabolic reactions to proceed with such remarkable rapidity even though the reactants may be in relatively dilute solution and are always at the low temperature corresponding to body temperature. Enzymes are proteins, usually conjugated proteins, and the protein moiety is always of endogenous origin. To what extent is the formation of these catalytic agents dependent on the character of the food supply? Even though many enzymes have been isolated as pure crystalline compounds a complete answer to this question must await the determination of the exact structure of the enzyme in its active form. Certainly, essential amino acids are always required in the form of dietary protein for the production of the protein component, the apoenzyme; frequently, if not always, mineral elements must be provided, either for incorporation into the structure of the molecule or to provide the necessary ionic environment for activity; for certain enzymes, those requiring coenzymes, vitamins are indispensable constituents of the coenzyme portion. The fact that all enzymes are not necessarily derivatives of vitamins does not in any way lessen the importance of this role for those vitamins that are in this category.

The relation of the structure of a vitamin to its specific role in catalytic systems is, of course, important for a complete understanding of vital phenomena. It is generally agreed that enzymatic catalysis results from the reversible formation of chemically unstable and therefore highly reactive intermediates. The picture is reasonably clear, at the molecular level at any rate, for vitamins that participate in hydrogen transport through the saturation of an unsaturated linkage, as in the case of riboflavin, or through the saturation of a double bond coupled with a shift from a quaternary to a ternary nitrogen, as in nicotinamide. Strangely, the reversible system, ascorbic acid-dehydroascorbic acid, which appears ideally suited to hydrogen transport and which can be shown to be active in oxidationreduction reactions in the laboratory, has not

been linked definitely as a part of a coenyzme in a biological system.

Pantothenic acid presents an especially impressive illustration of the unique role of a vitamin derivative in the metabolism of carbon compounds. It is a constituent of coenzyme A and through its sulfhydryl group forms thiol esters with acetic and other acids. Acetyl coenzyme A is the form in which the 2-carbon unit enters the citric acid cycle by adding to oxaloacetic acid to form citric acid. Most of the reactions involved in the building or degradation of the fatty acid carbon chains require the participation of coenzyme A. Lipoic acid also forms thiol esters with acetate after reduction of its disulfide bond and is one of the carriers of acetate as it moves from pyruvate to acetyl coenzyme A. Of interest is the fact that despite the many studies on the role of thiamine pyrophosphate in the decarboxylation of alpha-keto acids by carboxylase, the mechanism of action is still unknown. It has been suggested however, that thiamine also may be a carrier of "active acetate" and, possibly, this may be accomplished by the formation of a thiol ester after the opening of the thiazole ring.

Folacin, or pteroylglutamic acid, offers another stimulating example of the utilization of a vitamin derivative to form a labile intermediate, in this case an intermediate for the transport of a single carbon, "active formate." In this reaction folacin becomes formyl-tetrahydro-pteroyl-glutamic acid, also called the citrovorum factor or folinic acid. This is apparently the molecule in which single carbons are accepted and transferred for the building of the purine ring, of porphyrins and of non-essential amino acids. Furthermore, the formation of pyridoxamine by the reaction between pyridoxal and compounds possessing amino groups appears to explain the role of derivatives of vitamin B₆ in the catalysis of transamination and of certain other reactions of the individual amino acids, for example, the interconversion of serine and glycine and the formation of xanthurenic acid from tryptophan.

These examples of chemical mechanisms offer clear-cut evidence of the involvement of vitamin molecules in the reactions that are catalyzed by the respective vitamin-containing enzymes. No such clear-cut proof has been presented as yet for the similar activity of other vitamins of importance in human nutrition, viz., vitamin

 D_2 (or D_3), vitamin K, vitamin B_{12} and biotin. However, it appears reasonable to anticipate that most of these, if not all, will be shown to occur in enzymes and to function catalytically.

Earlier in this discussion it was stated that vitamins are not incorporated into the structural framework of the body if one assumes that cytoplasmic particles are not a part of this framework. This is, of course, a matter of semantics and the point needs some elaboration. Among the granules in the cytoplasmic gel are the microsomes and mitochondria. The latter are the larger particles and the principal carriers of the enzymes, including the vitamin-containing enzymes. There is every reason to believe that there is an orderly arrangement of these catalysts in the particles and that they afford the opportunity for concentration of the reacting compounds and for efficiency in a series of consecutive reactions [15].

It is axiomatic that the reproducible signs of a deficiency of a vitamin must be directly related to the breakdown of the mechanism in the cell in which the vitamin is an essential participating agent. In the instance of the lack of a vitamin such as thiamine, one should expect to find the symptoms of beriberi developing as the direct result of the impaired conversion of pyruvic and alpha-ketoglutaric acids, particularly, to their decarboxylated forms, acetic and succinic acids. Thiamine deficiency does, in fact, cause elevation of serum pyruvate levels. Opinions will vary regarding the significance of this finding inasmuch as beriberi has not been induced in an animal by the parenteral administration of pyruvate. Similar discrepancies are evident for each of the other nutrients when the clinical signs of an avitaminosis are compared with the abnormalities expected on the basis of the known participation of the vitamin in the catalysis of a metabolic reaction. The one clear instance of a direct physiological defect that is adequately explained by a vitamin lack is the impairment of vision in dim light as a result of a dietary deficiency of vitamin A or of its precursor, carotene. Here, the solution depends on the light-sensitive properties of vitamin A and of its aldehyde, retinene, on their occurrence in the pigments of the retinal rods and cones and on their influence on the photochemical processes of

What is the answer to this anomalous situation in which the incidence of onset and the clinical

manifestations of an avitaminosis seem to be so indefinitely related to biochemical findings of presumed importance? Can the difference in the incidence of deficiencies of niacinamide and of pantothenic acid be explained entirely by the differences in the natural occurrence of the two vitamins in foodstuffs? If riboflavin is intimately concerned with hydrogen transport and energy metabolism, why is not marked muscle weakness and prostration a primary sign of ariboflavinosis instead of a discolored tongue or cheilosis? How can one explain the frequency of changes in the skin in avitaminoses? Are genetic factors given sufficient consideration?

These questions are not asked because of any doubt regarding the reality of a vitamin-deficiency disease or the accuracy of published experimental observations. There is no lack of answers. It may be said that the clinical aspects of vitamin deficiencies are not mirrored in the biochemical or physiologic findings in studies on in vitro systems because deficiency diseases in man are frequently multiple deficiencies with or without caloric deficiency, the net result being a masking of individual manifestations. Or it may be said that dietary deficiencies are rarely absolute, rather that they are moderate and of long duration with time and chronicity as important factors. Or it may be said that vitamins are truly catalytic agents and are not used up, and that metabolism in vivo is only slowed, not stopped, as one may stop in vitro reactions. Or it may be said that homeostasis, the steady state, is maintained because the intact organism has available many opportunities for alternative pathways which tend to compensate for gross metabolic errors in single processes and thus may conceal them. Or it may even be said that each of these answers is true in part but that the real difficulty is the very human tendency to attempt to explain too much on the basis of research that has been magnificent in its achievements but inadequate in quantity.

In any event a continuing critical evaluation of the real significance of each of the clinical signs of avitaminosis is needed in order to be able to harmonize more satisfactorily the over-all physiologic response in the animal organism with the underlying biochemical abnormalities of single systems or of single tissues. Obviously, it is imperative to relate the clinical and physiologic aspects of avitaminoses in those conditions, rickets for example, in which there is still

no satisfactory demonstration of the specific biochemical activity and mode of action of the vitamin. Increased emphasis may well be placed on the search for methods of estimation of intermediate degrees of vitamin malnutrition. This is the same problem, not a different problem, as the search for ways to correlate more closely the biochemical findings and the physiologic responses to avitaminosis.

These remarks have emphasized man's accomplishments in his investigation of the physiologic role of the vitamins and, in addition, have noted certain problems which call urgently for further study. It is suggested that there is abundant evidence that a moderate degree of avitaminosis, even that which is barely detectable by clinical signs, may represent a much more severe breakdown of single intracellular reactions than has been supposed. Moderate malnutrition, therefore, should not be treated in a capricious fashion because the potential for ultimate deterioration under these circumstances is ever present as a sword of Damocles. All of experience and of experiment point insistently to the value of a dietary of nutritious foodstuffs in which vitamins and other essential nutrients are provided in the right amount and in the correct proportions.

REFERENCES

 HOPKINS, F. G. The dynamic side of biochemistry (abst.). Delivered to the Physiological Section of the British Association for the Advancement of Science, Birmingham. Lancet, 2: 851, 1913.

- 2. Hopkins, F. G. Feeding experiments illustrating the importance of accessory factors in normal dietaries. J. Physiol., 44: 425, 1912.
- LOHMANN, K. and Schuster, P. Untersuchungen über die Cocarboxylase. Biochem. Ztschr., 294: 188, 1937
- 4. McCollum, E. V. Who discovered vitamins? Science, 118: 632, 1953.
- HOPKINS, F. G. Diseases due to deficiencies in the diet. Lancet, 2: 1309, 1913.
- FUNK, C. On the chemical nature of the substance which cures polyneuritis in birds induced by a diet of polished rice. J. Physiol., 43: 395, 1911.
- of polished rice. J. Physiol., 43: 395, 1911.
 7. Holst, A. and Frölich, T. Über experimentellen Skorbut. Ein Beitrag zur Lehre von dem Einfluss einer einseitigen Nahrung. Ztschr. Hyg., 72: 1, 1912.
- OSBORNE, T. B. and MENDEL, L. B. The relation of growth to the chemical constituents of the diet. J. Biol. Chem., 15: 311, 1913.
- McCollum, E. V. and Davis, M. The necessity of certain lipins in the diet during growth. J. Biol. Chem., 15: 167, 1913.
- 10. Jansen, B. C. P. and Donath, W. F. Antineuritische. Vitamine. Chem. Weekbl., 23: 201, 1926.
- WILLIAMS, R. R. and CLINE, J. K. Synthesis of vitamin B₁. J. Am. Chem. Soc., 58: 1504, 1936.
- Peters, R. A. The biochemical lesion in vitamin B₁ deficiency. *Lancet*, 230: 1161, 1935.
- 13. Neuberg, C. and Karczag, L. Über zuckerfreie Hefegärungen. IV. Carboxylase, ein neues Enzym der Hefe. *Biochem. Ztschr.*, 36: 68, 1911.
- Auhagen, E. Über Co-Carboxylase. Reinigungsversuche und Vorkommen in tierischen Organen. Biochem. Ztschr., 258: 330, 1933.
- Green, D. E. Organization in relation to enzymic function. Symposium of the Society for Experimental Biology. Number x. Mitochondria and Other Cytoplasmic Inclusions, p. 30. New York, 1957. Academic Press Inc.

Some Clinical Aspects of Vitamin B Deficiencies*

W. H. Sebrell, Jr., M.D. New York, New York

The discovery that "water soluble B" consisted of more than one nutritional factor really opened a new era in nutrition and medicine. The vitamin B complex consists of a multiplicity of substances, several of which are of considerable clinical interest and importance. This discussion will be limited to the B vitamins which appear to be of most clinical importance at present. These are thiamine (vitamin B_1), niacin, riboflavin (vitamin B₂), cyanocobalamin (vitamin B₁₂), folic acid and pantothenic acid. The discovery, chemical identification and production in pure form of all these nutrients have resulted in great progress in our understanding of their biochemical and physiological actions. The clinical effect of thiamine, niacin and riboflavin in controlling beriberi, pellagra and ariboflavinosis has been so spectacular that these diseases are now almost curiosities in this country. In spite of this, our knowledge of the fundamental importance of these substances in maintaining the normal functions of the body through biochemical regulatory mechanisms is still very meager. The ready availability of these vitamins and their potent effect on the specific diseases mentioned have opened the way to studies on their mechanism of action. This phase of development of medical knowledge is now well underway and already offers some exciting possibilities, both in clinical and preventive medicine. In this connection, I would like to emphasize the importance of the distinction between vitamins as nutrients and vitamins as drugs. Although they may be used as drugs, the fundamental difference is that they are necessary for the normal functions of the body and are essential constituents of our food. In pure form they can be taken in relatively large amounts for long periods of time without physiological damage. As with all substances, even water, sugar or salt, vitamins taken in excessive and

unreasonably large doses may cause symptoms. However, these are for the most part so rare and difficult to produce that they are of little practical importance. The B vitamins taken in large doses may have pharmacological effects, a fact that could not be recognized until large amounts of pure vitamins could be given. Thus it has been shown recently that the administration of large doses of niacin will lower high blood cholesterol levels [1–3], an effect that was totally unsuspected as long as niacin was used only in amounts such as are found in foods.

We are all familiar with the classic clinical picture of beriberi, pellagra and riboflavin deficiency. I will mention them only briefly and devote most of this presentation to less clearly defined clinical problems resulting from B vitamin deficiencies. Historically, Lunin in 1881 found that substances other than sugar, fats, proteins and minerals were essential to life. Pekelharing in 1905 first demonstrated an unknown substance in milk of paramount importance in nutrition. Hopkins in 1906 concluded that milk contained accessory food factors. Eijkman in 1897 produced beriberi in pigeons by feeding them polished rice and cured the disease by feeding them the rice polishings. However, it was not until 1901 that Grijns showed that the effect was not a toxin, as suggested by Eijkman, but a deficiency of an essential substance. In the United States beriberi was looked upon as a disease of the rice-eating Orient until cases were found in Louisiana and South Carolina. About thirty years ago studies by several investigators, especially on alcoholic neuritis, uncovered the fact that there was a great deal of unrecognized beriberi in this country. Although the disease now appears to have largely disappeared in this country, there are still important clinical questions about thiamine deficiency which cannot be answered

^{*} From the Institute of Nutrition Sciences, Columbia University, New York, New York.

with certainty. Here is a substance, essential for the normal functioning of nervous tissue, which cannot be manufactured in the body and the requirement for which varies according to many factors, such as the total caloric intake and the amount of fat in the diet. The amount taken in food varies not only according to the kind of food but also according to the method of preparation, since thiamine is sensitive to heat and to alkali. Some of the non-specific but distressing aspects of thiamine deficiency are painful calf muscles, hyperesthesias of the extremities, loss of vibratory sense, constipation and loss of appetite due to atony of the stomach and intestines, enlargement of the heart and interference with the cardiac conduction system. Furthermore, it is exceedingly difficult to determine, even with the best laboratory work, whether or not the thiamine intake has been adequate. The vagueness of symptoms, the difficulties in diagnosis, and the uncertainty of the intake result in a situation in which we have many clinical reports of benefit from thiamine administration in a wide variety of clinical conditions, the true nature of which remain unproved.

In the case of pellagra and niacin, the situation is even more confusing. As with beriberi, pellagra appeared to be a clear-cut deficiency disease first recognized as such about 45 years ago in this country. Before 1907 it was thought to be a disease largely of Spain, Italy and southern France, and related to the consumption of corn. First described by Casal in Spain in 1735 pellagra, like beriberi, was first attributed to a toxin, although Mazari in 1810 suspected its deficiency nature. Goldberger in 1914 showed it to be a deficiency disease. The isolation of niacinamide by Elvehjem in 1937 and the demonstration that administration of niacin would cure and prevent the disease seemed to solve the problem from a clinical viewpoint. Actually it created more problems, many of which remain unsolved today. For example, we still have no understanding of the skin lesions of pellagra which are made more severe by exposure to sunlight, often bilaterally symmetrical or appearing like a necklace around the neck or across the nose and on the cheeks. Nor do we know why the mouth becomes sore and filled with organisms characteristic of Vincent's angina, or why hydrochloric acid disappears from the gastric juice. With pure vitamins available, it was possible to study the clinical syndrome

in detail; it was found that pellagra often consisted of a mixture of the symptoms of beriberi, ariboflavinosis and niacin deficiency.

Some confusing things about pellagra were clarified by the discovery that the amino acid, tryptophan, may be converted by the body into niacin and that man's niacin requirement is dependent on the amount of tryptophan in the diet. This finding has opened up an area of study of the balance between the B vitamins and amino acids, including vitamin B6. Although the fully developed syndrome pellagra is now rarely seen in this country, except as a complication of severe wasting disease or alcoholism, it is difficult for the physician to determine whether or not an individual has been receiving an adequate supply of niacin and tryptophan. It is well known that many pellagrins have severe mental depression and apathy; a few even develop a psychosis. Patients with disorientation, rigidities and symptoms of severe cerebral arteriosclerosis, but without the skin lesions of pellagra, have shown remarkable improvement after receiving large doses of niacin. It is therefore exceedingly difficult for the physician to determine in a case of malnutrition whether or not some of the vague symptoms may be due to a niacin-tryptophan inadequacy.

Ariboflavinosis is the third disease in man recognized as being due to a deficiency of one of the B vitamins. This condition was first identified in man in 1939 after the vitamin had been isolated and deficiency symptoms observed in experimental animals. The symptoms of seborrhea, scrotal dermatitis and fissures at the angles of the mouth are mild but the interstitial keratitis seen in some patients may cause blindness from corneal opacities. Although experimental animals die from riboflavin deficiency, no deaths in man have been recognized, and the nonspecificity of the lesions causes difficulty in the diagnosis of the deficiency. Riboflavin is an important constituent of living cells; it seems quite likely that further research will yield more data about its essentiality for man.

One of the most interesting of the B vitamins from a clinical viewpoint today is vitamin B_6 or pyridoxine. A great deal of animal experimentation demonstrated the physiological importance of this vitamin, and after its synthesis in 1939 biochemical research has shown that in its coenzyme form it is involved in a large number of the intermediary metabolic reactions of amino acids and fatty acids. However, it was not until 1948

that evidence of vitamin B₆ deficiency was seen in man. Hawkins and Barsky [4] observed changes in man on a vitamin B6-deficient diet for fifty-five days. In the next year it was shown that there was an increased excretion of xanthurenic acid after a test dose of tryptophan in subjects on a pyridoxine-deficient diet. The knowledge of what vitamin B6 deficiency might produce in man has been greatly extended by the work of Mueller and Vilter using the vitamin B₆ antagonist 4-desoxypyridoxine [5]. In patients receiving this antagonist seborrheic skin lesions, glossitis and lymphocytopenia developed. Snyderman and associates [6,7] published observations on two infants on a pyridoxine-deficient diet. The ability to convert tryptophan to nicotinic acid was lost and they stopped gaining weight. Convulsive seizures then developed in one and in the other there was a hypochromic anemia, both of which responded promptly to the administration of pyridoxine. The most convincing proof of the clinical importance of pyridoxine was accidentally provided by the study of several infants in whom convulsive seizures developed after receiving a commercially prepared infant formula in which much of the vitamin B6 was unintentionally destroyed in preparation [8–13]. Thus the importance of pyridoxine in the normal functioning of the central nervous system of man was dramatically demonstrated. Pyridoxine has been tried by a number of investigators in the treatment of epilepsy with conflicting and inconclusive results. Towers [14] has suggested the advisability of further therapeutic trials in seizure patients because the coenzyme of vitamin B₆, pyridoxal phosphate, functions in many of the metabolic reactions of glutamic acid. He suggests that pyridoxine deficiency may be associated with disturbances in the metabolism of the neural lipids of myelin structures. Pyridoxal phosphate appears to be essential for normal neuronal function and to be involved in the metabolic systems concerned in the seizure. The unusually high concentration of glutamic acid and glutamine in brain tissue as compared with other organs, and the fact that the central nervous system contains a unique metabolic system for the decarboxylation of glutamic acid to gamma amino butyric acid, which requires pyridoxal phosphate, further suggests the possible importance of this substance to the central nervous system.

In addition to this important function in the NOVEMBER, 1958

metabolism of nervous tissue, pyridoxine also plays a role in atherosclerosis in experimental animals. Rinehart and his associates [15,16] have produced degenerative changes in the arteries of Rhesus monkeys on vitamin B6-deficient diets along with other changes typical of vitamin B6 deficiency. These findings have been confirmed by Mushett and Emerson [17].

These observations have led Schroeder [18] and others to speculate on the possible role of pyridoxine deficiency in atherosclerosis in man. The work of Witten and Holman [19], which indicates that vitamin B6 is involved in the synthesis of highly unsaturated fatty acid from linoleic and linolenic acid, adds weight to such speculations in the light of recent work on the importance of unsaturated fatty acids in hypercholesterolemia. Another observation bearing on this problem is the effect of large doses of nicotinic acid in lowering blood cholesterol, which has already been mentioned. It should be noted that the niacin-tryptophan metabolic pathway is blocked unless vitamin B6 is also present. This is shown by an increased urinary excretion of xanthurenic acid which is one of the first indications of vitamin B6 deficiency. Failey [20] has given doses of vitamin B₆ to patients in an attempt to lower blood cholesterol, with very little effect. (The fall was significant at the 5 per cent level.)

The further clinical metabolic importance of vitamin B_6 to the nervous system is indicated by the observation that it is specific in combatting the neuropathy due to the administration of isoniazid [21–23].

There is increasing evidence that vitamin B₆ may also be involved in the prevention of dental caries. Rinehart first made note of the occurrence of dental caries in his monkeys on vitamin B₆-deficient diets. This observation has been most recently followed up with additional work by Strean which further indicates that vitamin B₆ deficiency may be a factor in dental caries in man. Strean and his associates [24,25] have shown that the addition of vitamin B6 to the diet has a suppressive effect on dental caries in the hamster and has a favorable influence on the oral microflora. The effect of vitamin B6 on caries in children is still being studied. They have reported a 40 per cent reduction in dental caries in twenty-eight children taking 3 mg. of pyridoxine for one year. These preliminary findings are being more thoroughly followed up.

The work of Wachstein and his associates on

the effect of vitamin B₆ in pregnant women is worthy of attention. They have observed that tryptophan metabolism is altered in pregnancy, as evidenced by an increase of xanthurenic acid excretion following a tryptophan load test; this is corrected by the administration of vitamin B₆. They have also noted that the metabolic change is greater in the toxemia of pregnancy [26–28]. It is to be expected with the large amount of new protein being formed during pregnancy that there would be a greater need for vitamin B₆ which plays such an important enzymatic role in protein metabolism.

I have dwelt at some length on vitamin B6 because of its clinical potentialities, although there is no clear-cut deficiency disease which can be related to it. It is indeed fortunate that it is widely distributed in foods. However, there are technical problems that make it difficult to estimate the human requirement or even to determine the vitamin B6 content of foods. The term vitamin B6 actually encompasses three substances, pyridoxine, pyridoxal and pyridoxamine. The enzymatically active form is pyridoxal 5-phosphate. The recommended daily intake of pyridoxine may be roughly estimated to be 1 to 2 mg. per day. However, since there is no entirely satisfactory method for the determination of the vitamin B6 content of various foods, it is difficult to determine whether or not an individual is meeting his entire needs. Therapeutic studies have indicated that quantities greater than 1 to 2 mg. are necessary for restoration of normal function. The possible role of this vitamin in convulsive states, its importance in both lipid and protein metabolism, and its possible effect on dental caries offer many fields of careful clinical study which could yield fruitful results.

Another important B vitamin which deserves much consideration is vitamin B_{12} . Since this is to be discussed elsewhere in this symposium in relation to anemia, I will mention it only briefly here because it deserves consideration in at least two areas other than anemia. First, I want to call attention to studies on its possible effect on growth in children. This has been studied by several investigators with varying results. Howe [30] has written an excellent review of the publications on this subject, with the conclusion that more carefully planned studies are necessary before a final answer can be given. Since vitamin B_{12} has been shown clearly to have an effect on growth in experimental

animals, it would appear likely that a vitamin B₁₂ deficiency in children produced either by insufficient intake or increased need would also cause retardation of growth. This question should receive a final answer.

The other area of clinical interest in connection with vitamin B₁₂ is its effect on neural tissue. Because the neurologic symptoms in pernicious anemia frequently respond so well to vitamin B₁₂ therapy, it has been tried in many other neurologic conditions. In several painful conditions, such as trigeminal neuralgia and herpes zoster, pain has quickly disappeared. Such results are always difficult to evaluate, but the relief seems clear enough to indicate that vitamin B₁₂ may be exerting some action on neural tissue. Experimental evidence in animals indicates that nucleic acid synthesis is reduced in vitamin B₁₂ deficiency. However, there is great need for more knowledge of the metabolic function of vitamin B₁₂, especially as it relates to lesions of the nervous system.

Another of the B vitamins concerned primarily with anemia is folic acid. Folic acid is a term which is used to designate a whole series of compounds, known as the pteroyl glutamates, which stimulate the growth of certain microorganisms. The term folinic acid, or citrovorum factor, refers to members of the series which also stimulate the growth of certain other specific microorganisms. These compounds, like other members of the B vitamin group, are important coenzymes in many intermediary metabolic reactions. Folic acid will correct the anemia of sprue, as well as pernicious anemia and some other megaloblastic anemias, but it does not have any beneficial effect on the neurological lesions of pernicious anemia.

The last of the B vitamins to which I want to call your attention is pantothenic acid. In contrast to the other B vitamins mentioned there are almost no clinical data available indicating any beneficial results from the administration of panthothenic acid. Yet the experimental evidence indicates that this is an essential metabolite. It is a part of coenzyme A, one of the most important of all the coenzymes. Deficiency of pantothenic acid in experimental animals results in serious lesions, especially of the adrenal glands. Pantothenic acid is widely distributed in nature, and it would seem that there should be some human abnormality related to a substance of such basic importance. Yet clinical studies have not revealed very much. Bean and his

AMERICAN JOURNAL OF MEDICINE

associates [31–34], using a pantothenic acid antagonist, omega methyl panthothenic acid, succeeded in producing clinical signs in normal young men. These signs were torpor, apathy and depression, cardiovascular instability, paresthesias, burning sensations, muscle weakness and other signs, including biochemical changes. They point out, however, that a low serum potassium could account for many of the changes, and it is not conclusively shown that they were dealing with an uncomplicated pantothenic acid deficiency. We are indeed a long way from an understanding of the possible role of this vitamin in clinical medicine.

In summary, then, we have examined briefly six of the B vitamins that are recognized as being of clinical importance to man. They are a widely divergent group of compounds on the basis of their chemical structure. However, they are close kin in that they are all essential; they all function as coenzymes, and several of them are known to be interrelated in the same intermediary metabolic pathway. Knowing as little as we do about them, it is clear that we cannot afford to be too dogmatic or fixed in our viewpoint about what they may or may not be capable of doing. It is just as unreasonable to assume that a patient has no deficiency of B vitamins unless he has full blown symptoms of beriberi, pellagra or ariboflavinosis as it is to assume that B vitamins in large amounts will prevent or cure a variety of vague and undiagnosed symptoms.

Now for some general considerations about the B vitamins and their use in clinical medicine. From what has already been presented, it should be clear that this problem is neither simple nor easily answered. It is easy to say with complete truthfulness that the consumption of an adequate diet, readily available in this country, will provide enough of the B vitamins from food sources to meet ordinary needs, especially since flour, white bread and corn meal are enriched with thiamine, riboflavin and niacin, which helps materially to meet the daily need. However, the patient usually consults his physician because he is sick. He may well have a condition that has seriously interfered with his consumption of a normal diet. This could be nausea and vomiting, diarrhea, anorexia, or just loss of teeth. Sometimes there may be conditions which have also increased his nutritional needs, such as infections, pregnancy, or an increased metabolic rate. Furthermore, the

situation may be rendered more difficult for the physician by the patient's inability to recall the details of his food consumption with sufficient accuracy to make possible even an approximation of his daily B vitamin intake. Therefore, if the physician suspects that deficiency of B vitamins may be complicating the patient's condition, about the only reasonable course at the present time is to prescribe a maintenance or therapeutic dose, as indicated. Here I want to stress as strongly as I can how important it is for the physician to advise his patient to eat an adequate diet. Most people eat largely by habit, tempered by the cost of food and according to taste. They are apt to know little about the B vitamin content of foods and are likely not to give nutrition a thought as they purchase food. The physician is in a powerful position to supply strong motivation necessary to change a lifetime of bad dietary habits. Dietitians, home economists, school teachers and others have been working for many years to improve the nutritional value of diets. They need the support of the family physician to make people appreciate the importance of good nutrition to health and to know what constitutes a nutritionally adequate diet. In the rehabilitation of any sick patient emphasizing the importance of good nutrition and how to obtain it by proper eating habits is one of the most valuable services which can be given to him by his physician. The physician also should recognize that many ill patients, dietary fadists or emotionally unstable individuals may not be able to obtain or to consume the foods necessary to furnish the needed B vitamins. In such cases, long continued vitamin supplementation may be the only practical answer.

There are other general clinical problems of a more controversial nature in which there may be a question of the adequacy of the B vitamin supply but the evidence is still too meager to draw any conclusions. First, the problems presented in pregnancy. I have already mentioned the indications that there may be an increased need for vitamin B6 because of the formation of protein. Pregnancy also constitutes a stress situation which increases the need for many nutrients. Furthermore, nausea and vomiting may reduce the nutrient intake, or the desire to avoid obesity may lead the pregnant woman to restrict her food supply unwisely so that she may be in a moderate state of deficiency just at the time that the nutritional

demands of the fetus are most important. Although the causes of human fetal malformations are not known, the effect of deficiency of B vitamins in producing congenital malformations in experimental animals has been clearly demonstrated [35]. Strean and Peer [35] have presented a little evidence which is suggestive of a relation between stress in pregnancy and the occurrence of cleft palate. I have already mentioned the importance of vitamin B_6 to the artificially fed infant. The physician should be certain that the vitamin B_6 content of prepared infant formulas is adequate.

Rapidly growing children present the most important problems in deficiencies of the B vitamins. Many years ago when pellagra and ariboflavinosis were widespread in the southern United States, these conditions were often found in children. Although they are rarely found today, special attention should be given to the B vitamin intake whenever there is failure

of proper growth and development.

In dealing with adults, particularly those of middle age, one of the physician's greatest nutritional problems is to prescribe a low calorie diet that is still adequate in vitamins. Obesity is widespread in this country, and many people now would like to reduce since they have read of the possible relation between obesity and heart disease, and between fats in the diet, blood cholesterol levels and coronary artery disease. It requires considerable care to devise a diet severely limited in calories which still retains an adequate supply of all essential nutrients including the B vitamins. A similar problem exists in regard to other therapeutic diets which the patient is to follow for a long period of time, such as those for diabetes, peptic ulcer, cirrhosis of the liver, and the like. Nutritional adequacy should always be in the physician's mind in designing such diets. Symptoms attributed to B vitamin deficiencies have been encountered often in all of these conditions.

In chronic diseases such as malignancy, tuberculosis, hyperthyroidism, cardiovascular disease and chronic alcoholism in which there is a loss of appetite, difficulty in eating or abnormal metabolic demand, symptoms of B vitamin deficiencies also have been found frequently and should always be looked for in their management.

In many acute conditions, especially those involving the stress of surgery and in which liquid diets or parental feeding may be required, special attention to the B vitamin supply is necessary to avoid depletion and possibly delay in convalescence.

Finally, a word about the aging individual. I have already referred to the effect of nicotinic acid in relieving the symptoms of cerebral arteriosclerosis even when no skin lesions of pellagra are seen. The lonely, inactive, aging individual, edentulous, lacking energy and often suffering the aches and pains of old age, presents a special problem in nutrition that can be one of the most difficult to manage. I mention the problem here only to urge that you keep the possibility of B vitamin malnutrition in mind as you care for them.

I have not tried to deal with the involved problem of the daily requirement of the B vitamins. This varies with age, sex, activity and other factors. The most authoritative, complete and up-to-date discussion is contained in the recently published revised edition of *Recommended Dietary Allowances* of the Food and Nutrition Board of The National Research Council. Therapeutic doses of the B vitamins necessary for treatment or repletion of a depleted individual are very much larger than maintenance doses and cannot be satisfactorily administered

except with vitamin preparations.

In conclusion I would like to emphasize three points. (1) The B vitamins are of great clinical importance even if we no longer see such obvious manifestations of severe depletion as beriberi and pellagra. (2) Physicians should always recommend that their patients follow food habits that will meet their B vitamin needs. (3) B vitamin supplementation should be used whenever the patient does not obtain his daily needs from his food.

REFERENCES

- PARSONS, W. B., JR., ANCOR, R. W. P., BERGE, K. Y., McKenzie, B. F. and Barker, N. W. Changes in concentration of blood lipids following prolonged administration of large doses of nicotinic acid with persons with hypercholesterolemia: preliminary observations. Proc. Staff Meet., Mayo Clin., 31: 377– 390, 1956.
- PARSONS, W. B., JR. and FLINN, J. H. Success of niacin and failure of niacinamide in reducing plasma cholesterol in patients with hypercholesterolemia. Circulation, 16: 499, 1957.

 Achor, R. W. P., Berge, K. G., Barker, N. W. and McKenzie, B. F. Treatment of hypercholesteremia with nicotinic acid. *Circulation*, 16: 499, 1957.

- Hawkins, W. W. and Barsky, J. Experiment on human vitamin B₆ deprivation. Science, 108: 284, 1948.
- 5. Mueller, J. F. and Vilter, R. W. Pyridoxine

 AMERICAN JOURNAL OF MEDICINE

- deficiency in human beings induced with desoxypyridoxine. J. Clin. Invest., 29: 193, 1950.
- SNYDERMAN, S. E., CARRETERO, R. and HOLT, L. E. Pyridoxine deficiency in human beings. Fed. Proc., 9: 371, 1950.
- SNYDERMAN, S. E., HOLT, L. E., JR., CARRETERO, R. and JACOBS, K. Pyrodoxine deficiency in the human infant. J. Clin. Nutrition, 1: 200, 1953.
- MOLONEY, C. J. and PARMELEE, A. H. Convulsions of infants as a result of pyridoxine (vitamin B₆ deficiency). J. A. M. A., 154: 405, 1954.
- COURSIN, D. B. Convulsive seizures in infants with pyridoxine-deficient diets. J. A. M. A., 154: 406, 1954
- MAY, C. D. Vitamin B₆ in human nutrition: a critique and an object lesson. *Pediatrics*, 14: 269, 1954
- Hunt, A. D., Jr., Stokes, J., Jr., McCrory, W. W. and Stroud, H. H. Pyridoxine dependency: a report of case of intractable convulsions in infants controlled by pyridoxine. *Pediatrics*, 13: 140, 1954.
- 12. Bessey, O. A., Adam, D. J. D., Bussey, D. R. and Hansen, A. E. Vitamin B₆ requirements in infants. Fed. Proc., 13: 451, 1954.
- Bessey, O. A., Adam, D. J. D. and Hansen, A. E. Intake of vitamin B₆ and infantile convulsions: a first approximation of requirements of pyridoxine in infants. *Pediatrics*, 30: 33, 1957.
- TOWER, D. B. Neurochemical aspects of pyridoxine metabolism and function. Nutrition Symposium Series, #12, p. 21, National Vitamin Foundation, 1956.
- RINEHART, J. R. and GREENBERG, L. D. Arteriosclerotic lesions in pyridoxine-deficient monkeys. Am. J. Path., 25: 481, 1949.
- RINEHART, J. F. and GREENBERG, L. D. Vitamin B₆ deficiency in rhesus monkey. Nutrition Symposium Series #12, p. 10, National Vitamin Foundation, 1956.
- MUSHETT, C. W. and EMERSON, G. Arteriosclerosis in pyridoxine-deficient monkeys and dogs. Fed. Proc., 15: 526, 1956.
- Schroeder, H. A. Is atherosclerosis a conditioned deficiency? J. Chron. Dis., 2: 28, 1955.
- WITTEN, P. W. and HOLMAN, R. T. Effect of pyridoxine on essential fatty acid conversions. Arch. Biochem., 41: 266, 1952.
- FAILEY, R. B., JR. Effect of large doses of pyridoxine on serum cholesterol in human. Circulation, 16: 506, 1957
- Biehl, J. P. and Vilter, R. W. Effect of isoniazid on vitamin B₆ metabolism; its possible significance in producing isoniazid neuritis. *Proc. Soc. Exper. Biol.* & Med., 85: 389, 1954.
- 22. PFEIFFER, C. C., JENNEY, E. H. and MARSHALL,

- W. H. Experimental seizure in man and animals with acute pyridoxine deficiency produced by hydrazides. *Electroencephalog. & Clin. Neurophysiol.*, 8: 307, 1956; *J. A. M. A.* (Abst.), 161: 1195, 1956.
- REILLY, R. H., KILLAM, K. F., JENNEY, E. H., MARSHALL, W. H., TAUSIG, T., APTER, N. S. and PFEIFFER, C. C. Convulsant effects of isoniazid. J. A. M. A., 152: 1317, 1953.
- STREAN, L. P., GILFILLAN, E. W. and EMERSON, G. A. Suppressive effect of pyridoxine as dietary supplement on dental caries in Syrian hamster. New York State Dent. J., 22: 325, 1956.
- STREAN, L. P., BELL, F. T., GILFILLAN, E. W., EMERSON, G. A. and Howe, E. E. The importance of pyridoxine in the suppression of dental caries in school children and hamsters. *New York State Dent.* J., 24: 133, 1958.
- 26. Wachstein, M. and Gudattis, A. Disturbance of vitamin B₆ metabolism in pregnancy. J. Lab. & Clin. Med., 40: 550, 1952.
- WACHSTEIN, M. and GUDAITIS, A. Disturbance of vitamin B₆ metabolism in pregnancy; influence of various amounts of pyridoxine hydrochloride under abnormal tryptophane load test in pregnant women. J. Lab. & Clin. Med., 42: 98, 1953.
- Wachstein, M. and Gudaitis, A. Disturbance of vitamin B₆ metabolism in pregnancy; abnormal vitamin B₆ load test. Am. J. Obst. & Gynec., 66: 1207, 1953.
- Wachstein, M. and Gaffeo, L. W. Influence of vitamin B₆ on the incidence of preeclampsia. Obst. & Gynec., 8: 177, 1956.
- Howe, E. E. Effect of vitamin B₁₂ on growth of retarded children. Am. J. Clin. Nutrition, 6: 18, 1958
- Bean, W. B. and Hodges, R. E. Pantothenic acid deficiency induced in human subjects. Proc. Soc. Exper. Biol. & Med., 86: 693, 1954.
- 32. Bean, W. B., Hodges, R. F. and Daum, K. Pantothenic acid deficiency induced in human subjects. J. Clin. Invest., 34: 1073, 1955.
- THORNTON, G. H. M., BEAN, W. B. and HODGES, R. E. The effect of pantothenic acid deficiency on gastric secretion and motility. *J. Clin. Invest.*, 34: 1085, 1955.
- 34. Lubin, R., Daum, K. and Bean, W. B. Studies of pantothenic acid metabolism. Nutrition Symposium Series, #12, p. 112, National Vitamin Foundation, 1956.
- WARKANY, J. Congenital malformations induced by maternal dietary deficiency. Nutrition Rev., 13: 289, 1955.
- Strean, L. P. and Peer, L. A. Stress as an etiologic factor in development of cleft palate. Plast. & Reconstruct. Surg., 18: 1, 1956.

Nutritional Anemias with Especial Reference to Vitamin B₁₂*

GRACE A. GOLDSMITH, M.D.

New Orleans, Louisiana

UTRITIONAL anemias probably constitute the most common nutritional disease in man, as stated in 1949 by Youmans [1]. Youmans also emphasized that the presence and severity of anemia are relatively easy to establish, a situation that does not hold for many other deficiency diseases, yet anemia often receives insufficient attention in medical practice. Differentiation of the nutritional anemias and determination of their pathogenesis present a more difficult problem, although much has been learned in recent years and many new diagnostic procedures have been developed. The nutritional anemias may be due solely to dietary inadequacy but more often are conditioned by some coexisting pathologic state that influences absorption, utilization or requirement of the nutrients essential for blood formation.

Theoretically, nutritional anemias could develop as a result of inadequate supply of any dietary factor which is required for the formation of erythrocytes or their constituents. From a practical standpoint, only a few nutrients have been shown to be important in the etiology of nutritional anemia in man, namely, iron, folic acid, vitamin B_{12} and ascorbic acid. Anemia is encountered frequently in association with severe protein deficiency but little is known of the pathogenesis of this condition. Anemia has been induced in experimental pyridoxine deficiency but has not been observed in clinical practice.

IRON DEFICIENCY ANEMIA

The nutritional anemia encountered most often throughout the world is that due to iron deficiency. This anemia may be due to an insufficient amount of iron in the diet but is more often the result of blood loss and an increase in iron requirement. Anemia due to inadequate

dietary supply of iron can occur at any time during the period of growth or in women prior to the menopause. It is common in women who have had frequent pregnancies and may be found in infants whose mothers were iron deficient, since fetal stores are dependent on maternal supply. In the adult male, nutritional anemia due to deficient iron intake alone rarely develops if body stores of iron are normal at maturity.

Iron appears to be absorbed in relation to need and little is excreted from the body. In normal adults, the daily iron loss except as blood is between 0.5 and 1.0 mg. daily [2]. The loss during menstruation if averaged over the twenty-eight-day cycle amounts to an additional 0.5 to 1.0 mg. daily. During pregnancy, the mother furnishes the fetus with 300 to 500 mg. of iron, or between 1.0 and 2.0 mg. a day. Moore [2] has shown that only 5 to 10 per cent of the iron in food is absorbed by adults who are not iron deficient; absorption is increased in iron deficiency anemia. Children absorbed a larger per cent of dietary iron than adults, absorption being related to the needs for growth [3].

Considerable evidence indicates that absorption may be regulated by the intestinal mucosal cell. According to the current hypothesis, iron combines with a protein, apoferritin, to form ferritin from which it subsequently is released into the blood stream. There it becomes attached to a specific protein, siderophylin or transferrin [4]. A number of factors influence the availability of iron in food. Ascorbic acid increases absorption, presumably by efficiently reducing ferric iron in food to the ferrous state [2]. Steatorrhea reduces the absorption of iron.

The diagnosis of iron deficiency anemia is seldom difficult since many procedures are

^{*} From the Nutrition-Metabolism Unit, Department of Medicine, Tulane University School of Medicine, and the Charity Hospital of Louisiana at New Orleans. The studies conducted in our laboratory which are reported in this paper were assisted by Grants from the Nutrition Foundation and the Division of Research Grants and Fellowships, U. S. Public Health Service (Grant A-1).

available for studying iron metabolism. The anemia of iron deficiency is characteristically hypochromic and microcytic. The serum iron concentration is low, usually less than 50 µg. per 100 ml. and the serum iron-binding capacity is increased. The bone marrow is normoblastic, and hemosiderin is found in minimal amounts. The latter may be estimated readily with a simple staining technic [5]. Radioactive iron may be used in determining absorption if this seems desirable. Iron deficiency due to blood loss is more common than deficiency due to poor dietary intake. In many instances both factors contribute to the development of anemia. The incidence of iron deficiency anemia is undoubtedly high even in this country although no precise data are available. The incidence in certain tropical areas is even greater and will be mentioned subsequently.

MACROCYTIC ANEMIAS

Anemias due to an inadequate supply of folic acid and vitamin B₁₂ have been widely studied in recent years. These anemias are characterized by macrocytosis, and the erythrocytes are well filled with hemoglobin. The bone marrow is megaloblastic and the peripheral blood shows leukopenia, multilobed polymorphonuclear leukocytes and thrombocytopenia. There is often an increase in red cell destruction with an elevation of serum bilirubin.

The etiology of these anemias is most complicated, and while much has been learned many problems remain for elucidation. The macrocytic anemia which has been studied most extensively is pernicious anemia, now known to be due to deficiency of vitamin B12. Search for the cause of pernicious anemia forms a most interesting chapter in medical history. After Minot and Murphy [6] had demonstrated that feeding large amounts of liver was effective in the treatment of pernicious anemia, Castle [7] showed that administration of beef muscle in combination with gastric juice from normal subjects would stimulate blood regeneration in pernicious anemia. The gastric juice of subjects with pernicious anemia was without effect. Castle postulated that an "extrinsic" factor in food combined with an "intrinsic" factor in gastric juice to form the antipernicious anemia factor of liver. Pernicious anemia developed because of absence of intrinsic factor in the gastric

When folic acid was discovered, it was thought

to be the antipernicious anemia factor since administration of this vitamin stimulated hematopoiesis in patients with pernicious anemia in relapse. However, hematologic remission was not maintained and neurologic lesions were neither benefited nor prevented. It was shown, also, that folic acid was neither the extrinsic nor the intrinsic factor of Castle.

Vitamin B₁₂ was isolated from liver by Rickes and associates [8] and independently by Smith [9] in 1948. The former investigators made use of a microorganism in their isolation procedure, Lactobacillus lactis Dorner, which seemed to require the antipernicious anemia factor of liver for growth [10]. Smith searched for the red pigment found in active fractions of liver extract. This pigment is now known to be the cobalt of the vitamin B₁₂ molecule. Shortly after its isolation, vitamin B₁₂ was demonstrated by West [11] and subsequently by many others to be the antipernicious anemia substance of liver. This vitamin will alleviate all manifestations of the disease including neurologic changes. Vitamin B₁₂ has also been shown to be the extrinsic factor of food [12].

Pernicious anemia results not from a dietary inadequacy of vitamin B₁₂ but from failure of absorption from the intestinal tract. Intrinsic factor appears to be necessary for absorption of vitamin B₁₂ in the amounts which are found in the average diet. The mechanism by which absorption is facilitated has not been elucidated in spite of intensive investigation, nor has the structure of intrinsic factor been determined. For a number of years it has been known that hog intestine has intrinsic factor activity but no satisfactory method of assay has been available. Materials could be tested for intrinsic factor activity only by administration in combination with vitamin B₁₂ to patients with pernicious anemia in relapse.

After vitamin B_{12} labeled with radioactive cobalt became available, a number of procedures were developed which are most useful in the assay of intrinsic factor and also in the differentiation of various types of macrocytic anemia. Three procedures have been used extensively in studying the absorption of vitamin B_{12} . In each a small dose of vitamin B_{12} , usually 0.5 to 2.0 μ g. labelled with Co^{60} or Co^{58} is administered. Following this, fecal excretion can be determined as proposed by Heinle [13] or by Mollin and associates [14], urinary excretion after a parenteral flushing dose of 1,000 μ g. of

NOVEMBER, 1958

non-labeled vitamin as suggested by Schilling [15], or radioactivity can be measured over the liver with the method developed by Glass [16]. The advantages and disadvantages of the several methods have been discussed recently [16]. Absorption of labeled vitamin B₁₂ has also been studied by determining radioactivity in blood [17,18].

Numerous investigators have used these procedures in studying vitamin B₁₂ absorption in the megaloblastic anemias [14,16,19-22]. On the basis of such tests these anemias can be divided into three main categories: (1) absorption of vitamin B₁₂ is minimal when the vitamin is given alone but is increased to normal when intrinsic factor is administered with vitamin B₁₂, (2) absorption is small or insignificant whether vitamin B₁₂ is given alone or in combination with intrinsic factor, (3) absorption is normal and intrinsic factor has no appreciable influence or may even decrease absorption if given in large amounts, as noted in normal subjects. The first category represents pernicious anemia; the second, malabsorption due to some cause other than absence of intrinsic factor and includes some subjects with tropical sprue, some with idiopathic steatorrhea, and others with a variety of intestinal abnormalities such as inflammation, diverticuli and resection. The non-specific term, malabsorption syndrome, has been applied to this group. The third category, that of normal absorption of vitamin B₁₂, is a most interesting one. In many instances these anemias may be due to folic acid deficiency, rarely to dietary deficiency of vitamin B₁₂. In other instances the cause of the anemia is obscure, as will be pointed out subsequently.

MACROCYTIC ANEMIA IN NEW ORLEANS

In the past few years more than a hundred patients with macrocytic anemia have been studied in the nutrition-metabolism unit at Tulane University. In addition to the usual medical, hematological and routine laboratory examinations, each patient has been subjected to a Schilling test [15]. In this test 2 μ g. of Co⁶⁰B₁₂ (0.5 μ c. radioactivity) was administered orally, followed in two hours by a parenteral injection of 1,000 μ g. of non-radioactive vitamin. Radioactivity was measured in the urine collected for twenty-four hours. A second test was carried out three days later at which time an intrinsic factor preparation of known potency was administered

with labeled vitamin B_{12} . Other procedures which were carried out in many subjects included estimation of the serum vitamin B_{12} concentration, glucose and vitamin A tolerance tests and fat balance studies. About half of the patients studied were found to be deficient in intrinsic factor and may be classified as pernicious anemia. In three subjects, deficiency of intrinsic factor was due to total gastrectomy.

Approximately one-fourth of the patients had malabsorption of vitamin B₁₂ not influenced by intrinsic factor. In eleven of these subjects the vitamin B₁₂ concentration was measured in serum prior to therapy. In each instance the concentration was extremely low, in the same range as that found in pernicious anemia. Some of the subjects had impaired absorption of glucose, fat and/or vitamin A while in a few instances absorption of these substances was normal. Almost all possible combinations of absorptive defects were observed. Achlorhydria after histamine stimulation was present in about one-third of the subjects and in most of these the diagnosis of pernicious anemia was made prior to the Schilling test. Some of the subjects were considered to have sprue on clinical grounds, some nutritional macrocytic anemia, and one idiopathic steatorrhea in view of a family history of a similar disorder. One subject had had an extensive intestinal reaction and one had regional ileitis with an ileotranscolostomy. In these last two subjects the malabsorption was due, presumably, to removal of the ileum which is believed to be the site of absorption of vitamin B_{12} [19]. The etiology of the malabsorption in the other subjects remains obscure. All of the patients responded to vitamin B₁₂ and some of them to folic acid. When folic acid was given initially, improvement followed addition of vitamin B₁₂ to the therapeutic regimen in several instances. No tests of folic acid absorption were carried out in these patients. Impairment of folic acid absorption has been observed in patients with findings similar to those noted in this series [23].

Many of the patients gave a history of eating a poor diet for long periods prior to the appearance of the malabsorption syndrome and anorexia frequently preceded glossitis, diarrhea or complaints referable to anemia. It is conceivable that prolonged dietary inadequacy of one or more essential nutrients could impair intestinal absorption. It would seem likely that such impairment would be temporary. In a number of these subjects, however, relapse

AMERICAN JOURNAL OF MEDICINE

occurred when vitamin B_{12} or folic acid therapy was discontinued. The persistence of absorptive defects after therapy with folic acid or vitamin B_{12} has been observed by many investigators in both tropical and non-tropical sprue [24,25]. It may be that sprue is an inborn error of metabolism, as suggested by Adlersberg [24], and that unknown trigger mechanisms are responsible for the appearance of the clinical syndrome.

Whether these patients should be classified as sprue (tropical or non-tropical) or idiopathic steatorrhea is a moot question. It is not known whether these syndromes are variants of a single underlying defect, since differentiation between them is far from precise. In only one subject was there a family history of celiac disease or steatorrhea. The response to a gluten-free diet was not tested in these subjects as satisfactory results were obtained without recourse to this regimen: moreover, this therapeutic test may not be specific for idiopathic steatorrhea. Similar pathologic lesions in the intestine have been reported in sprue and idiopathic steatorrhea. Until more is known about etiology, designation of this syndrome as idiopathic malabsorption seems desirable. The many facets of the malabsorption syndrome have been reviewed in a recent symposium [24].

Nearly one-fourth of the subjects studied by us had normal absorption of vitamin B₁₂ as judged by the Schilling test. The clinical diagnosis in these patients was sprue, nutritional macrocytic anemia or pernicious anemia in most instances. Two subjects had macrocytic anemia due to drug toxicity, one had macrocytic anemia associated with disease of the liver. In two subjects who had a sprue syndrome and in one in whom anemia was believed to be due to dietary inadequacy, the serum vitamin B₁₂ levels were extremely low. The two subjects with "sprue" responded to either folic acid or vitamin B₁₂ and relapsed when therapy was discontinued although the diet seemed to be adequate. Two subjects with "nutritional" macrocytic anemia likewise relapsed when treatment with vitamin B₁₂ was withdrawn. Neither of these subjects consumed a good diet.

The cause of anemia in some of these subjects may have been folic acid deficiency even though a response followed administration of vitamin B_{12} . However, low serum concentrations of vitamin B_{12} indicated deficiency of this vitamin in several subjects. Dietary deficiency of vitamin B_{12} is a most unlikely possibility. In studies

of vegans, that is of vegetarians who do not include any foods of animal origin in the diet, anemia is rare and even macrocytosis of pronounced degree is uncommon [26]. However, marked changes in the nervous system have been observed including subacute combined degeneration of the spinal cord. Only two cases of severe megaloblastic anemia due to dietary deficiency of vitamin B_{12} have been reported [27,28].

In some instances the anemia may have been due to temporary malabsorption which had improved prior to administration of the Schilling test. This would seem to be a tenable hypothesis in persons whose diet was extremely poor at intervals. It is tempting to postulate that in some instances a temporary decrease in formation of intrinsic factor may have occurred. Several subjects had achlorhydria after histamine stimulation. Another hypothesis might be that some additional unknown factor is needed for absorption of vitamin B₁₂ or folic acid and that this factor was missing in these subjects. Still another possibility is that the factor in serum which binds vitamin B₁₂ may have been present in insufficient quantities. It has been shown that most of the vitamin B₁₂ in serum is bound to protein. Some substantiation of several of these hypotheses has been obtained from in vitro studies carried out in our laboratory.

Miller [29] has shown that normal gastric juice, or materials with intrinsic factor activity prepared from hog intestine, will increase markedly the ability of serum proteins to combine with vitamin B12. This in vitro test has been applied in assaying the potency of intrinsic factor preparations and correlates well with in vivo assays with the Schilling technic and with assays conducted in patients with pernicious anemia in relapse. The in vitro test can be adapted also to estimation of the protein moiety of serum which binds vitamin B₁₂. Using these tests Miller, Unglaub and I have determined intrinsic factor activity and "serum factor" in a number of subjects with pernicious anemia, the malabsorption syndrome and macrocytic anemia with normal absorption of vitamin B₁₂ as judged by the Schilling test. The findings are given in Table 1. Intrinsic factor activity is expressed as millimicrograms of vitamin B₁₂ bound to protein per cubic centimeter of gastric juice. The activity of pooled, normal gastric juice in adult subjects has been found to range from 227 to 403 mug. with a mean value of 307 mug. The values

Table I
Intrinsic factor activity of gastric juice and serum
factor in patients with macrocytic anemia

Type of Anemia (according to Schilling test)	Sub- jects (no.)	Intrinsic Factor Activity (mµg. B12/cc. gastric juice)		Serum Factor (% normal)	
		Range	Mean	Range	Mean
Pernicious anemia Malabsorption syndrome	23	0-251 11-158	54 58	54-96 46-131	75 76
Normal absorption of B12	4	60-407	156	59-124	82

for individual subjects were also within this general range.

The values for serum factor are expressed as per cent of normal. Average normal values were obtained from analyses of pooled human serum, as well as of serum obtained from single control subjects.

All but one of the patients with pernicious anemia had values below normal for intrinsic factor activity of gastric juice. Only four subjects had intrinsic factor activity greater than $100~\text{m}\mu\text{g}$. B_{12} per cc. In addition, the quantity of gastric juice obtained in these subjects was extremely small in comparison to normal. The total intrinsic factor activity in twenty-four hours thus would be very low.

The variation in intrinsic factor activity among twenty-three patients with pernicious anemia suggests that varying degrees of deficiency of intrinsic factor may explain, in part, the duration of remissions in patients with this disease when therapy is discontinued. Another explanation is the amount of vitamin B₁₂ included in the diet. There is considerable evidence that vitamin B₁₂ is absorbed by two different mechanisms [30]. Amounts of just a few micrograms appear to require intrinsic factor whereas amounts of 25 to 50 µg, or more may be absorbed in the absence of intrinsic factor [30,31]. Doscherholmen and Hagen [30] found that absorption curves of labeled vitamin B₁₂ differed with the size of the dose administered. Delayed absorption with a peak concentration at eight hours was found with amounts of 0.5 to 10 μg.; rapid absorption with a peak concentration at four to six hours was observed with doses of 50 to 300 µg. Recent analyses of diets in our laboratory indicate that some may contain as much as 75 to 85 μ g. of vitamin B₁₂ per day, others as little as 1 µg. The larger quantities in

some diets might permit absorption of vitamin B_{12} without intrinsic factor.

The amount of vitamin B_{12} stored also may vary among subjects with pernicious anemia, even when comparable quantities have been administered parenterally. Miller and associates [32] have shown that intrinsic factor will stimulate the uptake of vitamin B_{12} by slices and homogenates of rat tissues. These findings suggest that intrinsic factor may be absorbed and function in the tissues to increase the combining of vitamin B_{12} with tissue proteins.

The intrinsic factor activity of the gastric juice of subjects who had the malabsorption syndrome was as low as that of the patients who had pernicious anemia. Some of the former subjects may have secreted larger quantities of gastric juice in twenty-four hours than did patients with pernicious anemia. Free hydrochloric acid was present in the gastric juice in some instances. Administration of gastric juice from several patients who had a malabsorption syndrome to patients with pernicious anemia, as part of the Schilling test, increased the absorption of vitamin B₁₂ to normal. Unfortunately, the intrinsic factor activity of this gastric juice was not measured simultaneously in vitro.

The interpretation of these findings is difficult. It seems unlikely that partial deficiency of intrinsic factor over a long period of time could lead to inability to absorb vitamin B_{12} even when intrinsic factor is supplied in adequate amounts. Deficiency of some other factor, as yet unknown, seems a better possibility. Miller and Hansen [33] have obtained evidence that a co-factor is needed for intrinsic factor stimulation of the uptake of vitamin B_{12} by tissue homogenates. A deficiency of this co-factor might explain malabsorption in some subjects.

In three of four patients who had normal absorption of vitamin B_{12} with the Schilling test, intrinsic factor activity was very low, less than $100~\text{m}\mu\text{g}$. B_{12}/cc . One of these subjects had been diagnosed as having sprue, one as nutritional macrocytic anemia and one as pernicious anemia. Two of these subjects relapsed when therapy was discontinued. The anemia in these subjects might be explained by a poor diet accompanied by lower than normal and perhaps fluctuating intrinsic factor production. At least one of these subjects appeared to be deficient in folic acid as well as in vitamin B_{12} .

A decrease in serum factor, that is in the

AMERICAN JOURNAL OF MEDICINE

protein moiety of serum that binds vitamin B_{12} , was found in a majority of patients with pernicious anemia and in some of the patients with other types of macrocytic anemia. In most instances the decrease was small, the majority ranging between 70 and 80 per cent of normal. Serum factor was less than 60 per cent of normal in only five subjects, two with pernicious anemia, two with malabsorption and one with normal absorption of vitamin B_{12} . Perhaps macrocytic anemia is occasionally due to an inadequate supply of serum factor. In view of the decrease in serum factor in many subjects it is conceivable that vitamin B₁₂ may stimulate formation of additional "receptor" protein when it is present in increased amounts.

MEGALOBLASTIC ANEMIA OF INFANCY

Megaloblastic anemia of infancy as observed in the United States has occurred in children who received diets inadequate in ascorbic acid [34]. The anemia responds to treatment with folic acid, rather than to ascorbic acid, but can be prevented with the latter vitamin. Occasionally vitamin B₁₂ is beneficial in this anemia. May [35] produced an anemia in monkeys which appeared to be comparable to megaloblastic anemia of infancy when diets low in folic acid and ascorbic acid were administered. Ascorbic acid prevented the anemia but folic acid was more effective therapeutically. In explaining the development of this anemia it has been suggested that ascorbic acid is necessary for the conversion of folic acid to folinic acid (citrovorum factor) or to the active form of folic acid.

In South Africa, Walt et al. [36] found an incidence of 9 per cent of megaloblastic anemia of infancy during a period of three months in which routine bone marrow examination was made on all case admissions. Eighty-nine per cent of these infants had Kwashiorkor. The authors suggest that protein deficiency, dysentery and other infections may play a major role in the etiology. The anemia was not due solely to protein deficiency, as megaloblastosis appeared during therapy with skimmed milk. When folic acid was administered the bone marrow became normoblastic in ninety-six hours, but hemoglobin did not increase rapidly.

Megaloblastic anemia develops occasionally in adults with severe scurvy. A few such cases have been reported in Africa [37]. Recently, Brown [38] reported an instance of megaloblastic

anemia responding completely to synthetic ascorbic acid alone, in a man who had scurvy and hepatic cirrhosis. The possibility that some defect in folic acid metabolism coexisted was considered.

MACROCYTIC ANEMIA OF PREGNANCY

The macrocytic anemia of pregnancy responds to folic acid in most instances and only rarely to vitamin B₁₂. This is true in both the temperate zones and the tropics [39,40]. In Malaya, Tasker and associates observed that megaloblastic anemias appeared to be due primarily to folic acid deficiency. The anemias were more common in women who were pregnant but were also seen in non-pregnant women and in men. Only 10 per cent of the women who were pregnant had very low serum vitamin B₁₂ concentration, i.e., less than 100 μμg./ml. A few subjects responded well to treatment with vitamin B₁₂ although the serum levels were in the normal range. Chanarin et al. [23] found low serum folic acid concentrations in pregnant women which appeared to be due to malabsorption of the vitamin rather than to dietary deficiency. It has been suggested also that an increased requirement of folic acid during pregnancy may explain the anemia in subjects on poor diets.

In South Africa, the majority of cases of megaloblastic anemia in Bantu and Indian patients were encountered in association with pregnancy or the puerperium [41]. Most of the subjects secreted free acid in the gastric juice and responded to treatment with folic acid. Serum B₁₂ levels were within the normal range.

Izak [42] studied the concentration of serum vitamin B₁₂ during pregnancy in women in Jerusalem. He found a decrease in the third trimester and an increase two to four weeks postpartum. The diets of these women had been low in animal protein before as well as during pregnancy. The incidence of anemia (less than 10 gm. hemoglobin/100 cc.) in a series of 2,500 women was 11 per cent. Of one hundred patients with anemia, a macrocytic blood picture with low serum vitamin B₁₂ levels was found in eleven . instances, and dimorphic anemia with low serum iron and vitamin B₁₂ levels in fifty-seven instances. The remaining patients had hypochromic, iron deficiency anemia. Malnutrition, increased requirement during pregnancy and frequent pregnancies were considered responsible for the deficiencies of iron and vitamin B_{12} .

In the tropics, vitamin B_{12} deficiency may more often be responsible for the anemia of pregnancy than in other regions. Normal serum vitamin B_{12} levels have been reported in the megaloblastic anemia of pregnancy in England and Scotland [43,44].

TROPICAL MACROCYTIC ANEMIA

Megaloblastic anemia is found not infrequently in certain areas of the tropics in nonpregnant women and in men. In the past, tropical macrocytic anemias were found to improve following administration of whole liver, autolysed yeast or crude liver extract. Failure of response to injections of refined liver extract was common or response was suboptimal and often required doses larger than those effective in pernicious anemia. Treatment with vitamin B₁₂ in large amounts was found to be more beneficial than liver extract but some patients responded slowly or not at all. In many studies administration of folic acid was found to result in excellent and complete remission. Recently, measurement of the serum vitamin B₁₂ concentration in subjects with tropical megaloblastic anemia has indicated that some of these anemias are due to vitamin B₁₂ deficiency [40]. In other instances, there appears to be a deficiency of both folic acid and vitamin B₁₂.

In a study of anemia in India and Africa, Foy and Kondi [45] concluded that the bulk of the tropical anemias are iron deficient and that neither protein malnutrition nor hookworm infestation plays a major role in their genesis. The anemias could not be cured by protein alone, although protein supplementation was needed for complete cure of some iron deficiency anemias. A small number of patients failed to respond completely to protein and iron, and improved when vitamin B₁₂ was given intramuscularly. Serum vitamin B₁₂ levels were in the normal range in these subjects. The authors postulate that the protein supplement increased the requirement of vitamin B₁₂. The main factors responsible for the high incidence of anemia appeared to be (1) poor absorption of iron on account of the type of diet eaten (high in phytic acid and phosphate and low in calcium) or (2) excessive dermal loss of iron on account of climate. In women, the high incidence was due to reproductive losses and to pregnancy occurring below the age of twenty years while growth and blood volume are still increasing.

In another report, Fov and Kondi [46] mentioned that 58 per cent of the anemias studied by them in Africa were megaloblastic, as compared to 15 per cent in India, and that megaloblastic anemia was nearly as common in males as in females. The megaloblastic anemias were of three types, responding to either penicillin, vitamin B₁₂ or folic acid, and were clinically and hematologically indistinguishable. They suggested that tropical megaloblastic anemia is associated with a diet "which produces an intestinal flora that competes for essential substances or one that is inimical to their synthesis." A complete response of some of these anemias to antibiotics substantiates this interpretation. Protein alone produced no specific response and the serum protein pattern was non-specific in these subjects. The presence of liver enlargement and the findings on liver biopsy were not correlated with the anemia.

Megaloblastic anemias associated with disorders of the small intestine, such as diverticulosis, stricture and anastomosis, resemble some of the anemias of the tropics in that they respond to treatment with antibiotics as well as to vitamin B_{12} or folic acid. The serum levels of vitamin B_{12} have been found to be low in these anemias and malabsorption of this vitamin, which is unaffected by intrinsic factor, has been demonstrated [47,48]. Bacterial interference with absorption of vitamin B₁₂ has been postulated as the cause of these anemias. The mechanisms by which an abnormal bacterial flora produce this effect are unknown. Anemia does not develop in all subjects with intestinal lesions. Perhaps body stores, dietary intake of vitamin B₁₂ and duration of the lesion influence the findings.

FOLIC ACID-VITAMIN B12 RELATIONSHIPS

A number of theories have been proposed to explain the interrelationships of vitamin B_{12} and folic acid in metabolism but data in support of these hypotheses are limited [49,50]. Both vitamins appear to participate at some stage in the synthesis of nucleoproteins. Folic acid, and perhaps vitamin B_{12} also, is involved in the transfer of single carbon units. However, the precise role of these two vitamins in blood formation is not known. Vilter's theory of the "mass action" effect of folic acid in producing improvement in pernicious anemia implies an ability to mobilize meager stores of vitamin B_{12} .

Several findings suggest that administration

AMERICAN JOURNAL OF MEDICINE

of either one of these vitamins may deplete body stores of the other. Treatment of pernicious anemia with folic acid leads to temporary improvement which is followed in most instances by hematologic, neurologic or glossal relapse. Harris [51] has reported that small daily doses of vitamin B₁₂ can aggravate signs of folic acid deficiency, i.e., glossitis and cheilosis.

Patients with pernicious anemia in relapse have less folic acid in the plasma and urine after administration of test doses than do normal subjects or patients in remission [50]. This may indicate a "conditioned" deficiency or an excessive demand for folic acid.

Nieweg and associates [52] reported that injection of vitamin B₁₂ in patients with pernicious anemia resulted in a fall in the folic acid activity of whole blood, followed by a rise after seventy-two hours. Tasker [53] observed a correlation between the vitamin B₁₂ concentration in the serum and urinary excretion of folic acid after a test dose in patients with severe megaloblastic anemia. Narayanan et al. [54] found that parenteral administration of vitamin B₁₂ produced a significant rise in serum folic acid in patients with nutritional macrocytic anemia, maximum levels being attained after three to seven days. Injection of folic acid in these subjects was followed by a rise in serum vitamins B₁₂ concentration with a peak level about the sixth day. The increase was augmented by prior therapy with vitamin B₁₂. It was suggested that a reciprocal relationship exists between vitamin B₁₂ and folic acid, and that large doses of one tend to mobilize the other from body stores. This may be a partial explanation of the response of some patients with megaloblastic anemia to either folic acid or vitamin B₁₂.

Meyer and associates [55] reported a lack of hematologic response to liver extract or vitamin B_{12} when a folic acid antagonist was given concomitantly to patients with pernicious anemia in relapse. This is additional evidence of the interrelationship of these two vitamins in hematopoiesis.

Certainly both folic acid and vitamin B₁₂ are needed for the prevention of the megaloblastic anemias. Complete understanding of the etiology and mechanisms responsible for the development of some of these anemias must await further research, both basic and clinical. Elucidation of the precise biochemical role of these vitamins in metabolism should assist in solving many of the remaining problems.

SUMMARY

Nutritional anemias are a common medical problem, particularly those due to iron deficiency. Megaloblastic anemias which respond to folic acid or to vitamin B_{12} are far from rare, even in the temperate zone, and are observed frequently in the tropics.

Anemias due to vitamin B_{12} deficiency are usually the result of malabsorption from the intestinal tract and only rarely of dietary inadequacy. The causes of malabsorption include lack of intrinsic factor in the gastric juice, lesions of the small intestine or an absorptive defect of unknown etiology that often involves other nutrients as well as vitamin B_{12} .

Anemia due to folic acid deficiency may be the result of a poor diet, malabsorption, increase in requirement or possibly defective utilization of this vitamin.

In a study of 100 patients with anemia in New Orleans, approximately half were found to have pernicious anemia as judged by the Schilling test and one-fourth a malabsorption syndrome which involved vitamin B₁₂ and usually other nutrients as well. In the remaining subjects the absorption of vitamin B₁₂ was normal but the anemia responded to vitamin B_{12} in most instances and often to folic acid as well. In these patients the clinical picture frequently resembled pernicious anemia or sprue. Hypothetical causes of this anemia are discussed. Data relative to the intrinsic factor activity of gastric juice and to levels of the factor in serum which binds vitamin B_{12} are reported for some of the subjects in each of the three groups.

Accurate diagnosis both as to the kind of anemia and its cause is essential if effective therapy is to be instituted. The diagnosis of iron deficiency anemia is seldom difficult. The newer technics permit determination of the primary etiologic factor in the macrocytic anemias in most instances even though mechanisms responsible for the development of some of these anemias remain obscure.

Acknowledgments: I wish to express appreciation to Drs. Amos Prevatt, Walter Unglaub, Fred Hunter and O. Neal Miller for their assistance in the investigations carried out in the Nutrition-Metabolism Unit at Tulane University. We are indebted to Dr. Nathaniel Ritter of Merck and Company who kindly furnished Co⁶⁰B₁₂ and non-radioactive vitamin B₁₂ for use in these studies.

REFERENCES

- YOUMANS, J. B. Some aspects of nutritional anemias. Wisconsin M. J., 45: 699, 1949.
- Moore, C. V. Nutritional factors in iron deficiency anemia. Scandinav. J. Clin. & Lab. Invest., 9: 292, 1957
- 3. Darby, W. J., Hahn, P. F., Kaser, M. M., Steinкамр, R. C., Densen, P. M. and Соок, M. B. The absorption of radioactive iron by children 7–10 years of age. J. Nutrition, 33: 107, 1947.
- Gubler, C. J. Absorption and metabolism of iron. Science, 123: 87, 1956.
- CARTWRIGHT, G. E., GUBLER, C. J. and WINTROBE, M. M. Specific functions of trace elements in blood formation. In: Methods for Evaluation of Nutritional Adequacy and Status, p. 111. Washington, D. C., 1954. National Academy of Sciences, National Research Council.
- 6. Minor, G. R. The development of liver therapy in pernicious anemia. *Lancet*, 1: 361, 1935.
- CASTLE, W. B., TOWNSEND, W. C., HEATH, C. W. and STRAUSS, M. B. Observations on the etiologic relationship of achylia gastrica to pernicious anemia. I-IV. Am. J. M. Sc., 178: 748, 764, 1929; ibid, 180: 305, 1930; ibid, 182: 741, 1931.
- RICKES, E. L., BRINK, N. G., KONIUSKY, F. R., WOOD, T. R. and FOLKERS, K. Crystalline vitamin B₁₂. Science, 107: 396, 1948.
- SMITH, E. L. and PARKER, L. F. J. Purification of antipernicious anemia factor. *Biochem. J.*, 43: 8, 1948.
- Shorb, M. S. Activity of vitamin B₁₂ for the growth of lactobacillus lactis. Science, 107: 397, 1948.
- West, R. Activity of vitamin B₁₂ in Addisonian pernicious anemia. Science, 107: 398, 1948.
- 12. Morgan, E. H., Hall, B. E. and Campbell, D. Hematopoietic activity of parenterally administered beef muscle concentrate. *Proc. Staff Meet.*, *Mayo Clin.*, 24: 594, 1949.
- Heinle, R. W., Welch, A. D., Scharf, V., Meacham, G. C. and Prusoff, W. H. Studies of excretion (and absorption) of Co⁶⁰-labeled vitamin B₁₂ in pernicious anemia. Tr. A. Am. Physicians, 65: 214, 1952.
- 14. Mollin, D. L., Booth, C. C. and Baker, S. J. The absorption of vitamin B₁₂ in control subjects, in Addisonian pernicious anemia and in the malabsorption syndrome. *Brit. J. Haemat.*, 3: 412,
- Schilling, R. F. Intrinsic factor studies. II. The effect of gastric juice on the urinary excretion of radioactivity after the oral administration of radioactive vitamin B₁₂. J. Lab. & Clin. Med., 42: 860, 1953
- GLASS, G. B. J. and BOYD, L. J. Differentiation of macrocytic anemias and diagnosis of pernicious anemia and sprue in remission by accelerated measurement of hepatic uptake of radioactive Co⁶⁰B₁₂. Ann. Int. Med., 47: 274, 1957.
- Doscherholmen, A. and Hagen, P. S. Radioactive vitamin B₁₂ absorption studies: results of direct measurement of radioactivity in blood. *Blood*, 12: 336, 1957.
- 18. BOOTH, C. C. and MOLLIN, D. L. Plasma, tissue and urinary radioactivity after oral administration of

- ⁵⁶Co-labeled vitamin B₁₂. Brit. J. Haemat., 2: 223, 1956.
- McIntyre, P. A., Sachs, M. V., Krevans, J. R. and Conley, C. L. Pathogenesis and treatment of macrocytic anemia. Arch. Int. Med., 98: 541, 1956
- Oxenhorn, S., Estren, S., Wasserman, L. R. and Adlersberg, D. Malabsorption syndrome: intestinal absorption of vitamin B₁₂. Ann. Int. Med., 48: 30, 1958.
- REISNER, E. H., GILBERT, J. P., ROSENBLUM, C. and MORGAN, M. C. Applications of the urinary tracer test (of Schilling) as an index of vitamin B₁₂ absorption. Am. J. Clin. Nutrition, 4: 134, 1956.
- Evans, J. R. The absorption of vitamin B₁₂ in the megaloblastic anemias. *Proc. Nutrition Soc.*, 15: 134, 1956.
- Chanarin, I., Anderson, B. B. and Mollin, D. L. The absorption of folic acid. *Brit. J. Haemat.*, 4: 156, 1958.
- The Malabsorption Syndrome. Edited by Adlersberg, D. New York, 1957. Grune & Stratton.
- GARDNER, F. H. and SANTIAGO, E. P. Oral absorption tolerance tests in tropical sprue. Arch. Int. Med., 98: 467, 1956.
- 26. Wokes, F. Anaemia and vitamin B₁₂ dietary deficiency. *Proc. Nutrition Soc.*, 15: 134, 1956.
- POLLYCOVE, M., APT, L. and COLBERT, M. J. Pernicious anemia due to dietary deficiency of vitamin B₁₂. New England J. Med., 255: 164, 1956.
- 28. Harrison, R. J., Booth, C. C. and Mollin, D. L. Vitamin B₁₂ deficiency due to defective diet. *Lancet*, 1: 727, 1956.
- MILLER, O. N. Studies on an interaction among serum protein, materials containing intrinsic factor and vitamin B₁₂. Arch. Biochem., 72: 8, 1957.
- 30. Doscherholmen, A. and Hagen, P. S. A dual mechanism of vitamin B₁₂ plasma absorption. J. Clin. Invest., 36: 1551, 1957.
- 31. Chalmers, J. N. M. and Hall, Z. M. Oral vitamin B₁₂ in pernicious anemia. *Brit. M. J.*, 1: 1179,
- MILLER, O. N. and HUNTER, F. M. Stimulation of vitamin B₁₂ uptake in tissue slices by intrinsic factor concentrate. *Proc. Soc. Exper. Biol. & Med.*, 96: 39, 1957.
- 33. MILLER, O. N. and HANSEN, H. Personal communication.
- MAY, C. D., Nelson, E. N., Lowe, C. W. and Sal-MON, R. J. Pathogenesis of megaloblastic anemia in infancy. Am. J. Dis. Child., 80: 191, 1950.
- 35. May, C. D., Hamilton, A. and Stewart, C. T. Experimental megaloblastic anemia and scurvy in the monkey. IV. Vitamin B₁₂ and folic acid compounds in the diet, liver, urine and feces and effects of therapy. *Blood*, 7: 978, 1952.
- Walt, F., Holman, S. and Naidoo, P. Megaloblastic anemia of infancy treated with folic acid. *Brit*. M. J., 2: 1464, 1957.
- 37. Bronte-Stewart, B. The anaemia of adult scurvy. Quart. J. Med., 22: 309, 1953.
- Brown, A. Megaloblastic anemia associated with adult scurvy: report of a case which responded to synthetic ascorbic acid alone. *Brit. J. Haemat.*, 1: 345, 1955.
- 39. Ungley, C. C. and Thompson, R. B. Vitamin B₁₂ and

AMERICAN JOURNAL OF MEDICINE

- folic acid in megaloblastic anemia of pregnancy and the puerperium. *Brit. M. J.*, 1: 919, 1950.
- Tasker, P. W. G., Mollin, D. L. and Berriman, H. Vitamin B₁₂ deficiency in the megaloblastic anaemias of Malaya. *Brit. J. Haemat.*, 4: 167, 1958.
- Syndromes in vitamin B₁₂ deficiency. Editorial. South Africian M. J., 31: 1107, 1957.
- IZAK, G., RACHMILEWITZ, M., STEIN, Y., BERKOVICI, B., SADOVSKY, A., ARONOVITCH, Y. and GROSS-OWICZ, N. Vitamin B₁₂ and iron deficiencies in anemia of pregnancy and puerperium. Arch. Int. Med., 99: 346, 1957.
- Mollin, D. L. and Ross, G. I. M. Vitamin B₁₂ deficiency in the megaloblastic anaemias. *Proc. Roy. Soc. Med.*, 47: 428, 1954.
- 44. GIRDWOOD, R. H. The megaloblastic anaemias. Quart. J. Med., 25: 97, 1956.
- FOY, H. and KONDI, A. Anaemias of the tropics: relation to iron intake, absorption and losses during growth, pregnancy and lactation. J. Trop. Med. & Hyg., 60: 105, 1957.
- Foy, H. and Kondi, A. Anemias of the tropics: East Africa with special reference to proteins and liver damage. Tr. Roy. Soc. Trop. Med. & Hyg., 52: 46, 1059
- HALSTED, J. A., LEWIS, P. M. and GASSTER, M. Absorption of radioactive vitamin B₁₂ in the syndrome of megaloblastic anemia associated with intestinal stricture and anastomosis. *Am. J. Med.*, 20: 42, 1956.
- 48. Scudamore, H. H., Hagedorn, A. B., Wollaeger, E. E. and Owen, C. A., Jr. Diverticulosis of the

- small intestine and macrocytic anemia with report of two cases and studies on absorption of radioactive vitamin B₁₂. Gastroenterology, 34: 66, 1958.
- 49. VILTER, R. W., HARRIGAN, D., MUELLER, J. F., JARROLD, T., VILTER, C. F., HAWKINS, V. H. and SEAMAN, A. Studies on the relationships of vitamin B₁₂, folic acid, thymine, uracil and methyl group donors in persons with pernicious anemia and related megaloblastic anemias. *Blood*, 5: 695, 1950.
- SPRAY, G. H. The role of pteroylglutamic acid and related compounds in macrocytic anaemia. *Proc. Nutrition Soc.*, 15: 119, 1956.
- HARRIS, J. W. Aggravation of clinical manifestations of folic acid deficiency by small daily doses of vitamin B₁₂. Am. J. Med., 21: 461, 1956.
- 52. NIEWEG, H. O., FABER, J. G., DE VRIES, J. A. and KROESE, W. F. S. The relationship of vitamin B₁₂ and folic acid in megaloblastic anemias. J. Lab. & Clin. Med., 44: 118, 1954.
- Tasker, P. W. G. Correlation of serum vitamin B₁₂ levels and urinary folic acid in nutritional megaloblastic anemias. *Lancet*, 2: 61, 1955.
- 54. NARAYANAN, M. S., SHENOY, K. G. and RAMASARMA, G. B. Reciprocal deviation in serum levels produced by injections of vitamin B₁₂ and folic acid in patients with nutritional macrocytic anemia. *Indian J. M. Sc.*, 11: 163, 1957.
- MEYER, L. M., RUIZ, N. D., CACCESE, A., RUIZKY, J., SAWITSKY, A. and BOCK, G. Studies in pernicious anemia patients treated with liver extract and folic acid antagonists. Am. J. M. Sc., 218: 197, 1040.

Diet in the Treatment of Liver Disease*

CHARLES S. DAVIDSON, M.D.

Boston, Massachusetts

TUTRITION relates to liver disease both as cause and effect. First, as to cause. In the protein depletion syndrome, known variously as kwashiorkor, malignant malnutrition, sindrome pluricarencial, a fatty liver is regularly found and is considered as the human counterpart [7] of fatty liver in experimental animals produced by diets low in protein (specifically choline and methionine) [2]. Alcoholics notoriously eat poorly and the poor diet-often high in calories, but poor in other nutrients, particularly protein and choline—undoubtedly is at least partly responsible for the fatty liver of alcoholics. Another hepatic lesion in alcoholics which may be caused by nutritional deficiency combines necrosis, "Mallory hyaline" [3] and polymorphonuclear infiltration and is a severe form of active hepatocellular disease [4]. Some of the reasons for suggesting that this lesion may be of nutritional origin will be related later. The exact relationship of poor diet, fatty liver and the so-called "Mallory lesion" to full blown cirrhosis† of the alcoholic has not yet been elucidated, although there seems little doubt that faulty nutrition over a considerable period of time is at least one factor in its pathogenesis. No attempt will be made here to cover the literature on nutrition as a cause of liver disease. Many excellent reviews and discussions of this subject may be consulted [2,5-8].

Faulty nutrition as a result of liver disease is well documented, although the reasons for it seem not to be understood entirely. When one considers a disease causing a nutritional disturbance it is customary to consider the effect of the disease, in this instance of the liver, upon ingestion, digestion and absorption, and intermediary metabolism of nutrients. Many patients with liver disease, such as acute hepatitis, chronic hepatitis, and cirrhosis of the alcoholic, suffer from anorexia, so that the ingestion of

nutrients may be greatly reduced unless measures are taken to insure their proper intake. It is probable that digestion and absorption of nutrients proceed with little noticeable reduction below normal in most forms of liver disease except in a few instances. Thus, the absorption of protein (measured by fecal nitrogen [9]), of carbohydrate, and of vitamins is thought to be sufficiently normal not to limit nutrition. Several recent studies have suggested defects in absorption of fat in some patients [10]. Most of these were alcoholics with cirrhosis, a condition which is often complicated by acute and chronic pancreatitis, so that deficiency of the external secretion of the pancreas may be the cause of poor digestion and absorption of fat. Impaired absorption of vitamin A may occur in some patients with liver disease and poor dark adaptation has been observed [11,12]

Although there are undoubtedly defects in the intermediary metabolism of carbohydrate, they are somewhat difficult to detect by present means and at any rate seem not to be gross enough to limit nutrition. The same is true of the intermediary metabolism of fat, although in severe parenchymal disease there are instances of severe lipemia, and body fat stores are usually greatly depleted in chronic liver disease. Measurements of lipids in the blood have failed to reveal striking or consistent abnormalities in patients with primary liver disease. Presumed abnormalities in the intermediary metabolism of protein and other nitrogenous substances are easier to document, for example, as severe hypoalbuminemia, frequent hyperglobulinemia, amino-aciduria, hyperammoniemia [9]. The severe muscle wasting characteristic of chronic cirrhosis is certainly evidence of protein deficiency which is by no means always dietary in origin.

Abnormalities in the intermediary metabolism of vitamins have been suggested by several observations. The relatively low concentration of diphosphothiamine in chronic cirrhosis was

[†] Cirrhosis is a pathologic change in the liver including formation of fibrous septa producing pseudo-lobulation and associated with nodular regeneration.

^{*} From the Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

established sometime ago [13]. The marked increase in the serum concentration of vitamin B₁₂ in active hepatic disease is likewise well documented [14]. Whether or not impaired storage of the various vitamins occurs is unknown, although the content of those most commonly stored by the liver, such as vitamin A, is usually reduced.

Abnormalities in electrolyte and water balance and metabolism in acute and chronic liver diseases are well documented. The tendency to water storage in acute hepatitis is well known and, of course, in chronic liver disease the occurrence of ascites and edema, often together with moderate hyponatremia and hypokalemia, are too well known to require further comment. Not so well known or well explained is the occasional occurrence of water intoxication, severe sodium depletion and severe potassium depletion in some patients.

Other evidences of altered mineral metabolism are found, particularly in relation to iron and copper. Hemosiderosis and hemochromatosis are the diseases in which an excess of iron has been deposited in the body, presumably from increased ingestion or absorption of this mineral. It seems clear also that the deposits of copper in the brain, liver and other tissues in Wilson's hepatolenticular degeneration also are due to an increased absorption of this element, but the cause for the increased absorption is not yet clear.

Diet in the Treatment of Viral Hepatitis. Acute infectious hepatitis in young people is almost always a self-limited disease and frequently by the time the patient enters the hospital with jaundice his appetite has returned and he can eat well. Some weight loss is common during the course of the illness. In the case of serum hepatitis the disease seems to have a more prolonged and insidious onset and is somewhat more severe and more often fatal, perhaps because these patients are usually suffering from some other illness for which icterogenic blood or plasma had been given as treatment. Viral hepatitis is likely to be more severe and prolonged in older persons. When nutritional depletion has occurred prior to the infection, it may be that a more prolonged illness results. At any rate, in the older person, in the case complicated by other illnesses, and in the patient already depleted, diet is important in treatment.

During World War II and during the Korean episode several studies relating dietary treat-

ment to prognosis in viral hepatitis were made. An extensive and controlled study was completed under the auspices of the Armed Forces Epidemiological Board and the Army Medical Service Graduate School [15]. It should be emphasized that this study was made on Army personnel, most of whom presumably had epidemic infectious hepatitis, which at that time was relatively benign and of short duration. The authors concluded that the optimal diet for the treatment of infectious hepatitis consists of about 3,000 calories, containing approximately 150 gm. each of protein and fat. Although fried and greasy foods may cause indigestion, the fat contained in meat, eggs and dairy products is not harmful and adds greatly to the palatability of the diet. During the stage of severe anorexia the patient should be urged to take frequent small feedings. Intravenous glucose should be administered if necessary to maintain a minimal caloric and fluid intake. The forcing of a high protein-high fat diet, by stomach tube if necessary, has been demonstrated to hasten recovery in most cases, but critically ill patients with fulminating disease or impending hepatic coma (see section "Hepatic Coma") may be harmed by excess dietary protein. Nevertheless, from this study and others it is concluded that in the uncomplicated patient with viral hepatitis, malnourished or not, a high protein-high caloric diet is the one of choice. The very ill patient should be watched carefully for the early signs of hepatic coma which will require complete revision of diet therapy.

Evidence for giving other than a normal diet to patients with chronic hepatitis is scanty. No clear evidence exists that one can shorten the course of chronic hepatitis, promote healing of the liver, or prevent further advance of the disease by alterations in the diet, specifically by forcing a high protein-high caloric diet, as is occasionally recommended. It seems reasonable for these patients to attempt to maintain body weight and nutritional status as near to normal as possible. This usually can be accompanied by the provision of a normal diet and its consumption by the patient concerned. The latter is not always easy to accomplish as anorexia may be a problem, sometimes a severe one for patients with chronic hepatitis.

Active Cirrhosis of the Alcoholic without Massive Ascites and without Hepatic Coma. A word might be said here concerning what is meant by the

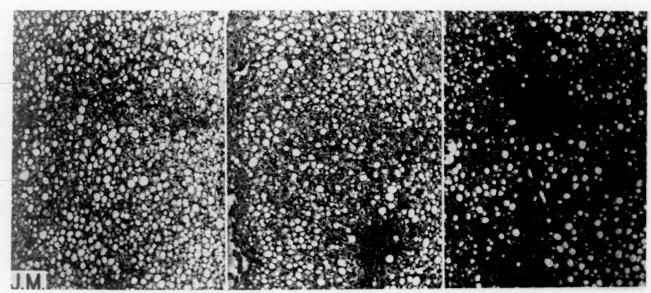


Fig. 1. Three liver biopsy specimens from one patient (left to right). Total time elapsed, twenty days. From: Phillips, G. B. and Davidson, G. S. Nutritional aspects of cirrhosis in alcoholism—effect of purified diet supplemented with choline. Ann. New York Acad. Sc., 57: 812, 1954.

term "active cirrhosis of the alcoholic." Clinically, these patients are usually jaundiced and have polymorphonuclear leukocytosis. Other evidences of hepatocellular disease, such as prothrombin deficiency, are quite common; whereas portal hypertension and its complications when present are usually not a major problem. Pathologically, fibrous tissue is usually present, but it is the hepatocellular disease which seems to be most important and is comprised of at least two abnormalities: (1) fatty change of the liver cells, and (2) parenchymal disorganization, focal necrosis, polymorphonuclear infiltration and intracellular hyalin (Mallory) which we have called collectively "the Mallory lesion." The fatty liver in the alcoholic and the clinical signs and symptoms associated with it usually show rapid progress toward healing, with reduction or even almost complete disappearance of the fatty change within two or three weeks. Such a rapid reversal is illustrated in Figure 1. Although provision of a normal diet is certainly good therapy in this situation, these patients may improve on a grossly deficient diet [16]. Occasionally patients with fatty liver fail to improve. When this occurs, the fatal termination is usually quite sudden and often unexplained, and occurs usually within a few days after admission to the hospital. The Mallory lesion and its response to dietary therapy has been much less studied. In fact, as noted earlier, its cause is unknown, although malnutrition may be

suspected as a causative factor. Based upon these assumptions, the provision of an adequate or normal diet is the treatment of choice.

Alcoholics are, of course, prone to deficiencies other than those presumed to be related to the liver disease. Malnutrition as evidenced by protein deficiency, beriberi, peripheral neuropathy, the Wernicke-Korsakoff syndrome, scurvy, and signs suggesting riboflavin deficiency are well known complications of severe and prolonged alcoholism. In addition, evidence has been presented which suggests that "rum fits," the spontaneous convulsions occurring during alcohol withdrawal in patients who are not epileptics, are due to vitamin B₆ deficiency [17]. This evidence is based upon an increased excretion of xanthurenic acid after tryptophane loading in these patients, which was abolished by the administration of 100 mg. of pyridoxine. Because of the frequent occurrence of these more specific nutritional deficiencies, all alcoholics, whether they have cirrhosis or not, should receive ample amounts of the vitamin B complex including thiamine, riboflavin, niacin and pyridoxine, and should be given vitamin C. This need be carried out only for a few days as a rule, as by that time deficiencies have been made up and the patient usually is able to consume a normal diet which will contain enough of these vitamins for maintenance.

Other than for these specific situations and conditions, no specific nutritional or dietary

therapy need be prescribed for these patients without ascites and edema and without evidences of hepatic coma. The provision and consumption of a normal diet is sufficient. As many of these patients have anorexia for a variable but usually short period of time, a considerable effort must be made by the physician and his aides during this period to see that food provided is actually eaten. After the first few days, these patients usually eat quite well.

Macrocytic anemia is a common accompaniment of liver disease. It is usually of mild degree and related to some diminution in blood formation and an increased rate of destruction [18]. No alteration in the diet is needed in this circumstance. Occasionally, however, severe megaloblastic anemia may be found in alcoholics with cirrhosis, due to a deficiency of folic acid. In this circumstance administration of folic acid per se will cause a rapid reticulocyte response and building of blood. Very occasionally pernicious anemia may accompany cirrhosis and here administration of vitamin B₁₂ parenterally

is specific. In contrast to patients with extrahepatic biliary obstruction, jaundiced patients with cirrhosis uncommonly have a prothrombin deficiency due to exogenous vitamin K absorptive failure. When prothrombin deficiency is found in these jaundiced patients, however, it is well to give a trial of intravenous infusion of 50 mg. vitamin K emulsion. This is helpful both as a liver function test and to permit therapeutic regeneration of prothrombin when there is occasional failure to absorb this vitamin. There is no evidence of vitamin E deficiency in cirrhosis in man, although in experimental animals vitamin E deficiency leads to massive hepatic necrosis and postnecrotic scarring.

Another relatively common accompaniment of cirrhosis of the alcoholic is parotid swelling [19]. Whether this is due to nutritional deficiency or not is unknown. The swelling resembles that which is seen in certain instances of starvation, particularly during feeding. The pathologic picture in both these instances is simply that of hyperplasia of the gland; no inflammatory changes have been observed. With improvement in the liver disease, decrease in size of the parotid usually occurs.

The patient with cirrhosis who has severe or prolonged anorexia, or has been vomiting or for some other reason cannot eat or eats very poorly, presents a more serious problem in dietary management. Many can be fed by tube using, for example, milk with sufficient added starch hydrolysate* to supply the caloric needs. Intravenous feeding with dextrose and protein hydrolysate is rarely necessary.

The Problem of Chronic Cirrhosis. By chronic cirrhosis is meant what one usually thinks of as typical "Laennec" cirrhosis. The patient does not usually have jaundice but shows severe undernutrition, ascites, abdominal collateral circulation, esophageal varices, leukopenia rather than leukocytosis, and other evidences of portal hypertension. Microscopically, the liver usually shows little or no fatty change. The Mallory lesion is not prominent, but nests of liver cells between interrupting bands of fibrous tissue predominate. Regeneration is usually evident and sometimes striking. The problem of ascites and edema and of sodium restriction will be discussed in the next section and, in the succeeding section, that of hepatic coma which may complicate any form of severe liver disease. In chronic cirrhosis uncomplicated by these two severe problems the provision and consumption of a normal diet is usually all that is necessary. When these patients have been alcoholics, they are often "reformed alcoholics," so that evidences of specific malnutrition syndromes are uncommon and replacement of possible vitamin undernutrition usually is not necessary. Undernutrition rather than malnutrition is the rule and is thought to result as much if not more from altered intermediary metabolism in this chronic disease than from impaired ingestion or digestion and absorption of foods.

As noted previously, there is some evidence for a defect in fat absorption. Some of these patients have diarrhea and, if careful study is made, steatorrhea may be found. This is probably due, in alcoholics at least, to associated pancreatic disease. In this circumstance the normal diet is well tolerated if additional pancreatin is administered. Sometimes the administration of pancreatin has been accompanied by rather dramatic improvement in the nutrition of these patients.

The Dietary Treatment of Ascites and Edema. In almost every patient with cirrhosis in whom ascites is a problem, accumulation of additional ascites and edema will cease when a diet severely restricted in sodium is provided [20]. The rate of

^{*} For example, Dextri-Maltose (Mead Johnson and Company, Evansville, Indiana) or Dexin (Burroughs Wellcome & Co., Tuckahoe, New York).

ascites and edema formation is best measured by daily body weight and abdominal circumference measurements. Both of these measurements usually stabilize within a day or two after sodium restriction is begun, restriction to 500 mg. or below in most instances. Generally, a diet providing approximately 200 mg. of sodium daily is advised. Most failures of the sodium restricted diet to halt the relentless formation of ascites, thus leading to inevitable paracentesis, are due to lack of knowledge of sources of sodium by the doctor, dietitian or patient, or lack of understanding of the necessity of severe restriction. Occasional patients must have fluid restriction also, as they are avid "water savers," but here the restriction of fluid is seldom to less than 1,500 to 2,000 cc. a day and rarely if ever to the point of thirst.

To achieve a diet so severely restricted in sodium and still to provide normal protein, vitamin and caloric intake requires the utmost cooperation of the patient, and study on the part of the physician and dietitian. The usual sources of sodium, such as table salt and salty foods, must of course be eliminated. Foods in which salt or sodium is added, either for preservation or for flavor, such as certain beverages, salted butter, margarine, and certain canned and frozen foods, cannot be used even in small amounts. Milk is another important source of sodium; the intake of this important source of nutrients can be continued by the use of either the powdered sodium-depleted milk product* or more recently by sodium-depleted milk manufactured by a few dairies in large cities and recently canned commercially,† Sweet butter must be provided; bread must be manufactured without added sodium. Labels on all canned and frozen foods must be carefully read and, if the sodium content is not listed, cannot be trusted. When in doubt, the physician sometimes must resort to analysis of purported sodium-depleted or restricted foods to determine their exact sodium composition. Many convenient books are now available for the patient taking a sodium-restricted diet, and help for physicians and dietitians is contained in a report by the National Research Council's Food and Nutrition Board [22].

* For example, Lonalac (Mead Johnson and Company, Evansville, Indiana).

Most patients, particularly those in whom ascites has been longstanding and in whom undernutrition is a problem, must be maintained on sodium restriction of this degree for considerable periods of time, usually months and occasionally even a year or two. If the sodium restriction is persisted in and the patient consumes an otherwise normal diet, one can expect, at least in cirrhosis of the alcoholic, a gradual gain in flesh and strength and sense of well being of the patient, together with a gradual loss of fluid accumulation. Along with this change usually goes a slow but progressive rise in the serum albumin concentration and a gradual return of many of the other liver function tests to or toward normal. This change is presumed to be due to liver regeneration. Figure 2 illustrates this change.

A few patients will begin to have a diuresis within a few days or a week or two after sodium restriction of this degree has begun. These are usually patients in whom the liver disease is beginning to improve fairly rapidly anyway, particularly the patient with acute cirrhosis in whom jaundice is fading and improvement is obvious.

After ascites has disappeared, many of these patients can again begin adding sodium gradually to their diet without gain in ascites or edema. Metabolic balance studies in these patients reveal that sodium balance is again achieved on an increased sodium intake; that is, the patient is able to excrete sodium again. Liberalization of sodium intake is usually begun first by liberalization of the meat allowance for the day. When this is well tolerated, regular milk is substituted for the sodiumrestricted milk product and then regular bread and finally, when the patient is surely doing well and gaining no weight, salt may be allowed on food and at the table and such foods as ham, bacon and salted butter may be cautiously attempted. Many patients, when improvement becomes pronounced and ascites is beginning to disappear, will develop ravenous appetites. This is usually a good sign, but if long continued, particularly in female patients, a tendency for fat accumulation may appear; in fact, obesity may become the problem.

Nitrogen balance is usually positive in patients with even extremely severe liver disease, although the degree of positivity usually increases (that is, more nitrogen is retained) as the severity of the disease diminishes during therapy. This

[†] The sodium is removed by passing the milk over exchange resins. Potassium is usually added and some vitamins are reduced in quantity [21].

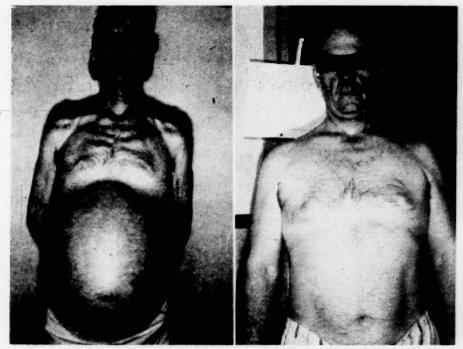


Fig. 2. Beneficial effects of protracted low sodium but otherwise adequate diet in a patient with cirrhosis and recurrent ascites. From: Davidson, C. S. J. A. M. A., 159: 1257, 1955 [20].

fact, together with the delayed clinical recovery of malnutrition in cirrhosis, compared to a similarly undernourished patient without liver disease leads one to believe that there are defects in the protein metabolism in liver disease [9]. Some of these are well documented, including the increased urinary excretion of amino acids and hyperammoniemia. The latter will be discussed together with hepatic coma in the next section.

Hepatic Coma. Although hyperammoniemia is a common accompaniment of hepatic coma, it has not been established as the causal factor; in fact, as will be seen, other unrelated conditions may precipitate coma. Presumably, most of the ammonia comes from the gastrointestinal tract, specifically the colon, from the action of bacteria on protein there. At the same time, other toxic materials, such as amines and phenols, may very well be produced and any one of them may be harmful, perhaps as much or more so than ammonia which thus far has been the only such compound extensively studied.

Hepatic coma may be precipitated in susceptible patients by gastrointestinal bleeding, severe infection, surgical operation, severe disturbances in fluid and electrolyte balance (specifically hyponatremia and hypokalemia and water intoxication), by such drugs as acetazolamide and chlorothiazide, by the oral or intravenous

administration of ammonium salts, and finally by protein in the diet [23]. Fortunately, most patients with liver disease, even when it is severe, are not susceptible to hepatic coma so that, for example, diuretics may be used and the protein in a normal diet or even a high protein diet, when desired, is harmless. Nevertheless, in a few susceptible patients the typical manifestations of impending hepatic coma will develop which will progress on to deep coma and even to a fatal termination when the protein in the diet is not tolerated. As already noted, the situation is frequently associated with hyperammoniemia, but not necessarily so. Some patients can tolerate as little as 50 gm. or less of dietary protein. This is particularly true of some patients after portacaval anastomosis [24]. For a more detailed description of hepatic coma and its treatment the reader is referred to several recent publications [23,25,26]. Emphasis here will be placed on dietary and antibiotic therapy.

It has been found that, if protein has been eliminated altogether from the diet or in some instances only reduced, the evidences of impending hepatic coma will often clear rapidly and the patient become quite normal again. This effect can be enhanced and prolonged by the oral administration of antibiotics, such as chlortetracycline and neomycin [27,28]. The

action of these antibiotics is presumed to be on the bacteria of the gastrointestinal tract, thus inhibiting the conversion of amino nitrogen to ammonia and perhaps other substances with absorption into the blood and subsequent toxicity to the brain and other tissues.

When a patient presents himself with impending hepatic coma or deep coma, one must first eliminate all possible precipitating factors, such as those listed. If severe electrolyte imbalance is observed, particularly hyponatremia after paracentesis, or severe hypokalemia, replacement therapy may be attempted and occasionally reversal of the comatose state may be accomplished. Most patients with hepatic coma have a moderate hypokalemia and probably have a tissue deficit. It is customary to administer 2 to 3 gm. of potassium to these patients if the urinary output is satisfactory. If the impending coma is mild, protein usually need not be restricted or withdrawn, but the oral administration of the antibiotic is begun at once. In this situation, improvement usually occurs within twenty-four hours and frequently the patient has regained a normal mental status and the typical flapping tremor of impending hepatic coma has disappeared within twenty-four to forty-eight hours. In the face of deep coma, however, it is still our custom to withdraw protein entirely from the diet and at the same time begin oral administration of the antibiotic. If the coma is reversible, as it frequently is, the patient generally awakens again within twenty-four to forty-eight hours. Protein administration is then cautiously begun. even though the patient may be somnolent or even semi-stuporous. Fluid and calorie intake are maintained by the administration of a starch hydrolysate* in water during the withdrawal period. When protein is begun again, we usually add a quart of milk in place of a quart of water; thus supplying about 30 to 40 gm. of protein. Following this, if the patient continues to improve, the protein content of the diet is gradually increased until a normal diet is again supplied, with the patient quite conscious. When neomycin is used we generally prescribe 6 to 8 gm. the first day, then reduce the dosage to 4 gm. daily until the patient is quite conscious. The dose is then gradually decreased further after the protein intake has reached normal. Some patients, particularly those in whom this

*For example, Dextri-Maltose (Mead Johnson and Company, Evansville, Indiana), or Dexin (Burroughs Wellcome & Co., Tuckahoe, New York).

syndrome develops after portacaval anastomosis, must be maintained on antibiotics for many months or longer. Neomycin appears to have a more prolonged effect with fewer complications than does chlortetracycline.

No mention has been made of the treatment of massive upper gastrointestinal bleeding, especially that from ruptured esophageal varices. The nutritional and dietary problems here relate to the feeding difficulty during or shortly after feeding, to the frequent occurrence of hepatic coma and to the concurrent treatment of ascites. During an acute episode of bleeding all food intake is stopped. As soon as possible, the gastrointestinal tract is emptied of blood by purges and enemas, and an antibiotic is given orally or by tube. Shortly thereafter, if the patient has stopped bleeding and maintains or regains consciousness, oral administration of protein may be begun, preferably in frequent small feedings, much as one would treat a peptic ulcer. Thus, alternating milk and antacids at hourly intervals seems good treatment. This is important, as in many patients it is difficult to decide whether bleeding is from ruptured varices, from gastritis or from a peptic ulcer, particularly in alcoholics. If cessation of bleeding continues and the patient's mental status remains normal or continues to improve, antibiotic therapy is continued and the protein content of the diet is gradually increased, much as it is in the treatment of hepatic coma uncomplicated by bleeding.

Little is known of the medical therapy of massive upper gastrointestinal bleeding in the interval between bleeding episodes. It is reasonable to assume, however, that frequent small feedings may be of value by reducing gastric acid which either may aggravate a peptic ulcer or possibly regurgitate, as some believe to be the case, into the lower end of the esophagus causing ulceration of varices. There is no direct evidence that this form of therapy will decrease bleeding episodes and it certainly is no substitute for more definitive treatment. Nevertheless, it seems rational and harmless to make this attempt.

A Note on Wound Healing. Although major surgery is generally poorly tolerated by patients with cirrhosis, surgical procedures are sometimes necessary. Granted recovery from the operation, it might be expected that a chronic debilitating disease such as cirrhosis might well compromise good surgical repair. This need not be the case,

AMERICAN JOURNAL OF MEDICINE

however, as indicated by wound healing generally by primary intention in a group of eleven patients subjected to herniorrhaphy [29]. In addition to careful preoperative preparation, anesthesia and postoperative care, preliminary treatment with a good food intake as long as possible before operation is certainly desirable. Healing of wounds by primary intention occurred in fifteen of sixteen operations, in spite of undernutrition and chronic liver disease with hypoalbuminemia, in this group of patients.

SUMMARY

In general, nutritional management of liver disease involves simply the provision of a normal diet. The exceptions are: (1) malnutrition associated with active cirrhosis of the alcoholic in which specific nutritional therapy may be needed; (2) the use of a sodium-restricted diet in the treatment of ascites and edema; and (3) the reduction of protein in the diet for patients with hepatic coma.

REFERENCES

- Davidson, C. S. Cirrhosis of the liver. Disease-a-Month, pp. 1–35. Sept., 1957.
- Schwarz, K. Nutritional factors and liver diseases. Ann. New York Acad. Sc., 57: 615, 1954.
- Mallory, F. B. Cirrhosis of the liver. New England J. Med., 206: 1231, 1932.
- PHILLIPS, G. B. and DAVIDSON, C. S. Acute hepatic insufficiency of the chronic alcoholic. Clinical and pathological study. Arch. Int. Med., 94: 585, 1954.
- LEEVY, C. M. Nutritional factors in liver disease in man. Am. J. Clin. Nutrition. Submitted for publication.
- RATNOFF, O. D. and PATEK, A. J. The natural history of Laennec's cirrhosis. *Medicine*, 21: 207, 1942.
- HARTROFT, W. S. and RIDOUT, J. H. Pathogenesis of the cirrhosis due to choline deficiency; escape of lipid from fatty hepatic cysts into biliary and vascular systems. Am. J. Path., 27: 951, 1951.
- KLATSKIN, G. The role of alcohol in the pathogenesis of cirrhosis. Yale J. Biol. & Med., 26: 23, 1953.
- Gabuzda, G. J. and Davidson, C. S. Protein metabolism in patients with cirrhosis of the liver. Ann. New York Acad. Sc., 57: 776, 1954.
- 10. Fast, B. B., Wolfe, S. J., Stormont, J. M. and Davidson, C. S. Fat absorption in alcoholics with cirrhosis. To be published.
- RALLI, E. P., BAUMAN, E. and ROBERTS, L. B. Plasma levels of vitamin A after the ingestion of standard doses: studies in normal subjects and patients with cirrhosis of the liver. J. Clin. Invest., 20: 709, 1941.
- PATEK, A. J. and HAIG, C. The occurrence of abnormal dark adaptation and its relation to vitamin

- A metabolism in patients with cirrhosis of the liver. J. Clin. Invest., 18: 609, 1939.
- WILLIAMS, R. H. and BISSELL, G. W. Thiamine metabolism with particular reference to the role of the liver and kidneys. Arch. Int. Med., 73: 203,1944.
- 14. LEAR, A. A., HARRIS, J. W., CASTLE, W. B., and FLEMING, E. M. The serum vitamin B-12 concentration in pernicious anemia. J. Lab. & Clin. Med., 44: 715, 1954.
- CHALMERS, T. C., ECKHARDT, R. D., REYNOLDS, W. E., CIGARROA, J. G., DEANE, N., REIFENSTEIN, R. W., SMITH, C. W. and DAVIDSON, C. S. The relative effects of strict bed rest and dietary components in the treatment of acute infectious hepatitis. J. Clin. Invest., 32: 559, 1952.
- ECKHARDT, R. D., FALOON, W. W. and DAVIDSON, C. S. Improvement of active liver cirrhosis in patients maintained with amino acids intravenously as the source of protein and lipotropic substances. J. Clin. Invest., 28: 603, 1949.
- LERNER, A. M., DECARLI, L. M. and DAVIDSON, C. S. The association of pyridoxine deficiency and convulsions in alcoholics. To be published.
- Jandl, J. H. The anemia of liver disease: observations on its mechanism. J. Clin. Invest., 34: 390, 1955.
- WOLFE, S. J., SUMMERSKILL, W. H. J. and DAVID-SON, C. S. Parotid swelling, alcoholism and cirrhosis. New England J. Med., 256: 491, 1957.
- DAVIDSON, C. S. Cirrhosis of the liver treated with prolonged sodium restriction: improvement in nutrition, hepatic function and portal hypertension. J. A. M. A., 159: 1257, 1955.
- Council on Foods and Nutrition, American Medical Association. Statement on low-sodium milk. J. A. M. A., 163: 739, 1957.
- Food and Nutrition Board. Sodium restricted diets.
 The rationale, complications and practical aspects of their use. National Academy of Science
 —National Research Council Bulletin 325, 1954.
- 23. Davidson, C. S. Hepatic coma. Advances Int. Med., 7: 33, 1955.
- 24. McDermott, W. V. and Adams, R. D. Episodic stupor association with an Eck fistula in the human with particular reference to the metabolism of ammonia. J. Clin. Invest., 33: 1, 1954.
- SHERLOCK, S., SUMMERSKILL, W. H. J., WHITE, L. P. and PHEAR, E. A. Portal-systemic encephalopathy. *Lancet*, 2: 453, 1954.
- McDermott, W. V., Jr. Metabolism and toxicity of ammonia. New England J. Med., 257: 1076, 1957.
- SUMMERSKILL, W. H. J., WOLFE, S. J. and DAVIDSON, C. S. The management of hepatic coma in relation to protein withdrawal and certain specific measures. Am. J. Med., 23: 59, 1957.
- FAST, B. B., WOLFE, S. J., STORMONT, J. M. and DAVIDSON, C. S. Antibiotic therapy in the management of hepatic coma. Arch. Int. Med., 101: 467, 1958.
- YONEMOTO, R. H. and DAVIDSON, C. S. Herniorrhaphy in cirrhosis of the liver with ascites. New England J. Med., 255: 733, 1956.

Some Aspects of Nutrition and the Kidney*

ROBERT M. KARK, M.D., F.R.C.P. (LONDON)

Chicago, Illinois

THE kidneys, particularly the proximal tubules of the nephrons, are the guardians of the nutritional wealth of the body. Each day, for example, nearly 2 kg. of ascorbic acid are filtered through the walls of the glomerular tuft into the renal tubules, and all but a few milligrams are returned to the bloodstream. The excretion of ascorbic acid in the urine is determined by the plasma level, the rate of glomerular filtration, and the maximum rate of tubular reabsorption [1]; and of these functions, the latter is crucial in preventing urinary wastage of the vitamin [2]. The extraordinary efficiency of the proximal tubules in defending the body against loss of water-soluble vitamins, glucose, amino acids and other nutrients is more than matched by the lower reaches of the nephron which act to conserve water and electrolytes. Even in chronic renal disease when large amounts of dilute urine are passed each day, there is little or no excessive loss of ascorbic acid, and conditioned deficiencies of water-soluble vitamins are extremely uncommon complications of renal failure.

The extraordinary reabsorptive capacity of the proximal tubules in health and disease is one reason why measurement of the urinary output of nutrients—particularly of the water-soluble vitamins—is of little value in the diagnosis of the classic deficiency diseases. Twenty years ago we thought differently; the vitamins were just beginning to be synthesized, and most clinicians interested in nutrition were seeking methods of diagnosing pellagra, beriberi and scurvy in the laboratory. The so-called subclinical forms of these diseases were thought to be important, and we believed that a vitamin deficiency might be brought to light by measurement of its urinary excretion, particularly after injection of a test dose.

In animals, disturbances of renal function and structure have been produced with some difficulty by dietary manipulations. Nocturia, hematuria, renal calculi and tubular abnormalities have developed as a result of inadequate food intake. Thus far, deficiencies of ascorbic acid, vitamin K, vitamin A, alpha-tocopherol, linoleic acid, choline, potassium, magnesium and chloride have been shown to affect the kidneys of animals—usually the tubules [3]. The pathologic changes have not always been clearcut, perhaps due to present-day difficulties in interpreting structural abnormalities in tubular cells by tinctorial technics.

In man suffering with severe chronic malnutrition, renal function is disturbed and reduced. The most commonly described features are polyuria with hyposthenuria [4,5], but when the patient dies of starvation little is found in the kidney but atrophy. The most severe type of protein malnutrition is found in infants and children all over the world and particularly in the tropics. The clinical manifestations are described under a variety of names, including marasmus, atrophy, athrepsia, Melnahrschaden and kwashiorkor. In these conditions the kidneys secrete a copious dilute urine [6]. Maximal conservation of solute suggests that the renal tubule cells are functioning as effectively as possible [7]. Although gross structural changes are not often seen in kidneys of malnourished infants and children coming to autopsy, some have been reported and reviewed by Davis [8]. These consist of intense fatty metamorphosis in the cells of the convoluted tubules. This seems to be a constant finding, while other changes which have been reported are inconsistent, and their importance is uncertain. There are no characteristic renal changes in pellagra and beriberi. Scurvy and hemorrhagic hypoprothrombinemia are the only deficiency states known to produce hematuria. Until the recent description of kaliopenic nephropathy there has been no real evidence to indicate that defi-

* From the Departments of Medicine, Presbyterian-St. Luke's Hospital, Cook County Hospital, and the Research and Educational Hospitals, and the University of Illinois College of Medicine, Chicago, Illinois. Supported in part by a grant from the U. S. Public Health Service (H-2253) and by a contract with the Department of the Army, Office of the Surgeon General (DA-49-007-MD-637).

ciencies of other nutrients seriously affect renal structure and function in man. This is surprising, since the kidneys are second only to the liver in synthetic activities and in other biochemical functions which serve the body. Despite their need for protein and nutrients to carry on their varied metabolic activities, they appear to be relatively resistant to the effects of nutritional deprivation. Their immunity to nutritional disease is probably related to their unique position in the nutritional economy of the body. They are small organs, but in an active man they receive over 3,000 L. of blood each day—one-sixth of the cardiac output and one-sixth of the circulating nutrients.

Two years ago a symposium on "Nutrition and the Kidney" appeared in The American Journal of Clinical Nutrition [7-17], and what has been added to our knowledge since then has been published recently in The American Journal of Medicine. These articles reviewed the milkalkali syndrome [18], kaliopenic nephropathy [19], and the clinical patterns of tubular dysfunctions [20]. In recent months Stanbury [21] has also reviewed the disorders of renal tubular, function in a most thorough manner. The older literature, what little there was of it, deals in the main with the effects of high or low protein diets on renal hypertrophy and repair after nephrectomy, or on the short-term effects of different diets on renal function, and has been completely reviewed by Smith [22].

It has been known for some time that an excessive intake of vitamin D can produce hypercalcemia, hypercalcuria and metastatic calcification in the kidney, which may lead either to fatal or reversible renal failure [12]. Dietary imbalance, with a high calcium, low phosphorus diet, has been shown to promote renal lithiasis [23], particularly in hot, dry climates.

In recent years it has been suspected that an excessive intake of common table salt was a factor in the production of essential hypertension. The relationships between sodium intake and the kidney have been explored recently by Meneely and his colleagues [24] who have produced renal lesions and hypertension in rats by feeding them diets containing large amounts of salt. Hartroft and Hartroft [25] have also demonstrated interrelationships between levels of dietary salt, the activity of the juxtaglomerular apparatus of the kidney, and the glomerulosa (aldosterone-producing) layer of the adrenal cortex. Obviously the relationship of salt intake

to the development of essential and other forms of hypertension, such as eclampsia, is one of the most important unsolved nutritional problems of our day and age; and Dahl [26] has recently reviewed the literature on salt intake and salt need, and their bearing on hypertension.

Best and Hartroft [27] have produced hypertension and renal disease in adult rats by an acute deprivation of choline during infancy, the rats being fed at a luxus level during their life span. This observation, coupled with Hartroft's [28] finding of glomerulosclerotic-like deposits in the kidneys of choline-deficient rats, raises once again the question of the etiology of the renal complications of diabetes, long suspected of being dietary in origin. In the kidneys from diabetics one nearly always finds the commonplace arteriolar nephrosclerotic lesions, as well as the pathognomonic nodular and diffuse lesions of diabetic glomerulosclerosis [29]. In the past, renal arteriosclerosis has been considered to be part of the aging process but attempts have been made recently to equate the many forms of vascular disease with a high intake of saturated fats. Certainly most of us prescribe a diet rich in fats for our diabetic patients, and on general principles one wonders whether this is wise.

In this paper I do not propose to review further the literature on nutrition and the kidney. Instead, some observations made by my colleagues and myself will be presented which stem directly from Dr. Youmans. The work was initiated by him, or directed by him, or is being carried out under his aegis.

RENAL CONSERVATION OF ASCORBIC ACID IN THE COLD

During World War II there existed a belief that in cold climates soldiers required more ascorbic acid than usual to maintain health. Scurvy has always been known as a disease par excellence of the sailor and of the sojourner in high altitudes, and from time immemorial its development has been related to cold, damp, fatigue, and the hard work of arctic and sea travel. Even Lind [30], after he had discovered that oranges and lemons cured scurvy at sea, emphasized the importance of cold as an etiologic factor in scurvy.

Bachstrom [31] was the first to indicate that cold played no part in producing the disease. He had studied and reported on an epidemic of scurvy which, appearing in the height of the summer of 1703, decimated 5,000 of the be-

sieged inhabitants of Thon, in Prussia. Epidemic scurvy occurs in Central Africa [32] and other tropical countries [33], and in 1917 it appeared in soldiers during the siege of Kut-al-Amara,

Iraq, during World War I [34].

Soon after the beginning of World War II, Dr. Youmans assumed responsibility for the nutritional health of the United States Army. Through Dr. W. Hurst Brown, a close liaison was formed with the Canadian Army, and joint studies were planned to investigate the interrelationships of nutrition, health and physical fitness of Allied soldiers in all parts of the world [35-37]. Dr. William Bean took charge of an American team; I, a Canadian team; and both were joined by Dr. Robert E. Johnson of the Harvard Fatigue Laboratory, who had designed equipment and tailored laboratory methods to quantitate physical fitness and to measure urinary and blood vitamins and proteins of soldiers in the field [38]. One of the problems put to us concerned the requirements of ascorbic acid for soldiers living in the cold, and among other studies we tried to determine whether there was a significant renal conservation of ascorbic acid in cold climates. While carrying out nutritional surveys and testing rations, the serum and urinary excretion of ascorbic acid of thousands of soldiers was studied in temperate climates, in the mountains, and in desert, tropic and arctic areas. In one experiment run in the middle of the winter, thirty-two soldiers acclimatized to a hot climate were flown overnight from Florida (75°F.) and were left to fend for themselves in the middle of the Canadian prairie with the temperature at 40°F. below zero [39]. A wide variety of packaged and fresh rations were tested, including a pemmican ration designed by V. Steffanson [40]. The data on ascorbic acid excretion were plotted as distribution curves. None of these field studies indicated renal conservation of ascorbic acid in the cold, nor did they show any remarkable change in ascorbic acid metabolism due to exposure to the cold [41-43]. These findings were later confirmed by studies in the laboratory [44].

DIABETIC NEPHROPATHY AND DIET

In the United States nodular glomerulosclerosis has been found in 17 to 36 per cent of diabetic patients dying in hospitals, and diffuse glomerulosclerosis and arteriolar hyalinization is even more common [29]. Most of the pathologic lesions of diabetes, including the specific

renal lesions, can be explained on the hypothesis of widespread deposition, particularly in and around the blood vessels, of protein-carbohydrate complexes which are present in abnormal amounts in the blood of patients with the disease. The problem is to decide whether the lesions are complications of diabetes which might be avoided by diet, or whether they are concomitant changes, the tendency towards which is inherited separately. Unfortunately there is as yet no clear-cut answer. We know of no incontrovertible evidence that specific renal lesions of diabetes can be prevented by strict control of the disease. The rarity of glomerulosclerosis in "acquired diabetes," such as Cushing's syndrome, and the difficulty of producing it in experimental animals are points against it being a complication and in favor of its being a concomitant of "idiopathic" diabetes. Against this view and in favor of the complication theory are the apparent rarity of glomerulosclerosis before 1923, the year of the introduction of insulin, and the fact that our studies [29] indicate that the incidence of renal involvement differs considerably in different parts of the world. For example, in a series of 200 diabetic patients attending a university teaching hospital in East Africa, no cases were found of established renal disease, and only one of gangrene [46]. Of 145 diabetic patients attending the Tohoku University Hospital in Japan, 26.8 per cent had persistent proteinuria, and 8.6 per cent had the "Kimmelstiel-Wilson syndrome" [47]. These latter figures are comparable to what might be found in the United States. The typical Japanese diet (low fat, high carbohydrate) is similar to that of East Africans and differs from that of Americans. The common feature distinguishing the Americans and Japanese from East Africans appears to be the availability of insulin, which raises the possibility that the lesions are caused by the kidneys' reaction to injections of exogenous insulin. However, we have found nodules in sections of a renal biopsy specimen from one patient who, we were quite sure, had never received insulin. There are also a number of reports in the literature of patients with typical nodular lesions in whom the diagnosis of diabetes was not made during life; presumably they too had never received insulin.

ECLAMPSIA AND DIET

Save for the changes of malignant nephrosclerosis which appear late in the disease, as yet no unique histologic abnormalities have been

found in the kidneys of patients with essential hypertension studied by autopsy or through renal biopsies [48–50]. However, the renal lesions of pre-eclampsia-eclampsia are unique, and their histology has been thoroughly studied with my colleagues, Doctors Victor Pollak, John Nettles and Conrad Pirani [51]. Because accurate clinical diagnosis of this condition is often difficult, even in primiparous patients whose optic fundi are said to be characteristic of eclampsia, percutaneous renal biopsies were made in fifty women with toxemia of pregnancy. Exact diagnoses were made in all: five had primary renal disease; ten, arteriosclerotic lesions; and in the remaining thirty-five, lesions of pre-eclampsia were found.

The glomeruli were the seat of the characteristic histologic lesions in pre-eclampsia. They were enlarged, appeared edematous and ischemic, and often completely filled Bowman's capsules. The swelling affected both epithelial and endothelial cells and was more severe in the former. The whole of each glomerulus was affected, and all glomeruli were involved to a like degree. There was no thickening of the glomerular basement membrane. In most instances the juxtaglomerular apparatus was readily seen. Serial biopsy studies were made in a number of patients before and after parturition. In these cases the renal abnormalities disappeared after delivery of the child. As compared with most renal diseases, one of the unusual features of the histologic picture of pre-eclampsia was the uniformity of the change seen in the glomeruli throughout each section. In most renal diseases such as diabetic glomerulosclerosis, glomerulonephritis or lupus nephritis, involvement of the glomeruli is spotty. In sections from patients with these diseases it is usual to find that some glomeruli may be perfectly normal and that the remainder are altered to different degrees by the specific disease process which involves them. The uniform nature of the glomerular changes in preeclampsia and the close resemblance of the pathologic features from case to case implies that the lesion may be caused by a uniform type of neurogenic stimulus which affects all glomeruli equally or, as is more likely, by a uniform metabolic or nutritional abnormality.

The clinical pattern and the geographic distribution of the pre-eclampsia-eclampsia reminds one of pellagra. Epidemic outbreaks occur in various parts of the world. The disease is endemic in some areas, and the sporadic

cases which we see in large cities tend to appear in the poor, the ignorant and in those whose nutrition has been disturbed by food fads or for other reasons. Theobald [52] was among the first to draw attention to its peculiar geographic distribution and to relate its appearance to nutritional factors. He recalls that when he was in charge of the largest obstetric service in the city of Bangkok, Siam, he saw only eight cases of eclampsia from 1926 to 1929. When he moved to Ceylon, the situation was quite different. The incidence there was twenty-eight per thousand live births and was probably the highest in the world. On returning to Great Britain he found that the mortality rates were higher in Scotland than in England or Wales. He also noted that the incidence of eclampsia doubled in Hong Kong during 1941 when gross malnutrition was rife as a result of the war. On the other hand, pre-eclampsia increased in Belgium and Holland after their liberation from German occupation, at a time when food became more plentiful.

There is a marked variation in the incidence of pre-eclampsia in different areas of South Africa [53]. In Capetown, where four groups of people live under distinct social and economic conditions, eclampsia is common in the Cape Malays and less common among the Bantu, Cape Colored and European population groups [54]. The Cape Malays are moslems, artisans and fishermen. They are descendants of slaves brought to South Africa from Java and Malaya in the eighteenth century, and they have an unusual pattern of food intake [55] as well as characteristic methods of preparing their diet [56].

Recently Wachstein [57] and others have suggested that the metabolism of vitamin B6 is altered in pregnancy, but it does not appear to me that a simple deficiency of this vitamin is responsible for the specific lesion of the kidney in pre-eclampsia. It appears more likely that the lesion may be the result of a very complex metabolic disturbance involving abnormal placental hormones, an unbalanced dietary intake, and a high intake of salt. Be this as it may, the recognition and description of the pathognomonic renal lesion of pre-eclampsia allows us to make exact diagnoses by renal biopsy. This discovery will permit us to characterize accurately the disordered biochemical pattern in those who have pre-eclampsia and will provide a sound basis for the study of the nutritional aspects of the renal disorder.

SYNTHETIC DIETS FOR CHRONIC RENAL FAILURE

At present the physician who deals with renal disease is mainly concerned with methods of protecting the patient from the nutritional ravages resulting from damage to the kidney. In the last year, following on Kolff's development of a "disposable" artificial kidney [58], it has become popular to treat patients ill with chronic renal disease and uremia—particularly those with exacerbations of glomerulonephritis or renal infection—by hemodialysis.

In the past few years my colleague, Dr. Derek D. Gellman, and I [59] have used a rather simple device to restore nutritional balance in these patients. A suitable synthetic liquid diet is prepared and delivered to the patient by a pump through an indwelling gastric tube at a constant rate day and night [60]. Because the diet is delivered drop by drop and at a slow, steady rate, it has been used successfully in patients who are vomiting. An example of its usefulness follows:

A. L., a five year old girl, was ill with chronic renal failure and secondary bone changes as a result of small congenital cystic kidneys and secondary pyelonephritis. When first seen by us she was semi-comatose and dehydrated, and looked at the point of death, having been vomiting for some days. The most recent blood estimations (several days previously) had been nonprotein nitrogen, 164 mg./100 ml.; potassium 5.7 mEq./L.; chloride, 118 mEq./L.; carbon dioxide, 7 mM./L.; calcium, 8.4 mg./100 ml.; and phosphorus, 4.2 mg./100 ml. The most pressing need was to replace the water and electrolytes lost in the vomit, but in view of the fact that she had renal failure we decided to give no phosphate and only small quantities of potassium until the serum level of this latter electrolyte was known. A Mead-Johnson tube was passed, and a synthetic mixture containing the following was fed slowly and continually for the next eighteen hours:

Sodium	********	227 mEq.
Potassium		25 mEq.
Calcium		40 mEq.
Chloride		165 mEq.
Bicarbonate and lactate		127 mEq.
Glucose		250 gm.
Distilled water		

By the next morning there was no clinical improvement except that the child had ceased to vomit. The results of chemical estimations on blood taken immediately before treatment was started were now available. They were: non-protein nitrogen, 160 mg./ 100 ml.; sodium, 124 mEq./L.; potassium, 2.5 mEq./L.; chloride, 89 mEq./L.; carbon dioxide, 12 mM./

L.; and calcium, 4.4 mg./100 ml. Those for the second day were: sodium, 147 mEq./L.; potassium, 2.5 mEq./L.; chloride, 111 mEq./L.; and carbon dioxide, 16 mM./L. Clearly the sodium and chloride replacement was adequate, but she was still deficient in potassium, bicarbonate and calcium. It was decided to give for the second twenty-four hour period the following mixture:

Sodium	30 mEq.
Potassium	75 mEq.
Chloride	
Bicarbonate and lactate	115 mEq.
Calcium	
Magnesium	
Glucose	
Distilled water	2,000 ml.

During the day the child had a number of tetanic spasms for which she was given injections of 10 per cent calcium gluconate. The next morning she was transformed. She was fully conscious, bright-eyed, sitting up in bed asking for breakfast. She had not vomited since tube feeding had started, and the tetany had stopped. The blood chemical findings were: non-protein nitrogen, 124 mg./100 ml.; sodium, 145 mEq./L.; potassium, 3.7 mEq./L.; chloride, 110 mEq./L.; carbon dioxide, 23 mM./L.; and calcium, 6.4 mg./100 ml.

The child lived happily for another eighteen months before azotemia became so severe as to be uncontrollable, and she died.

QUANTITATIVE HISTOCHEMISTRY OF THE NEPHRON

In 1939, soon after niacin became available for the treatment of pellagra, Dr. Sydenstricker demonstrated to me a young woman, ill with pellagra, who was also thought to have pyelonephritis. She was unusual because her daily requirements for the vitamin were fantastically high. Unless her intake was kept over 500 or 600 mg, of nicotinic acid per day she broke out in a typical pellagrous rash. The opinion expressed at that time was that her requirements for niacin had been raised to abnormal levels by reason of infection. Having seen a large number of alcoholics with pellagra and severely infected septic wounds recover from their nutritional deficiency state on small doses of niacin, I was somewhat skeptical, and since that time have looked for similar cases to study, but unfortunately have found none. In 1956 Dent and his colleagues [61] described in the Hartnup family a hereditary pellagra-like skin rash with unusual amino-aciduria and bizarre biochemical features. They speculated that the findings might be the result of abnormal metabolism or requirements for niacin. In addition, a renal tubular

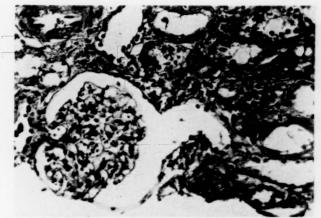


Fig. 1A. Renal biopsy specimen from a patient with hepatolenticular degeneration (Wilson's disease). Adjacent serial sections through glomerulus and the surrounding tubules. Bowman's space can be seen opening into the proximal convoluted tubule. Note that the lining epithelium of the first part of the proximal convoluted tubule is flattened and resembles that of Bowman's capsule. Only at a distance from the glomerulus does the lining epithelium begin to be cuboidal. Hematoxylin and eosin, original magnification × 425.

defect was found, and this is of particular interest to us because tubular defects fail to conserve filtered nutrients and are a prime renal cause of deficiency diseases.

Fanconi [62] first proposed the concept that a defect in the tubular cells could account for the clinical syndrome which bears his name. Children afflicted with this disease have a genetically inherited abnormality in which a histologic defect in the proximal tubule is associated with defective tubular reabsorption and wastage of glucose, amino acids and phosphates. The latter disturbance leads to rickets or osteomalacia, depending on the age of the patient. Fanconi's name has become generally used as an eponym [63] to describe the various types of "tubular failure," such as "the adult Fanconi syndrome" and "the secondary Fanconi syndrome," which occur in patients ill with pyelonephritis or multiple myeloma. A wide variety of clinical syndromes have been described as the result of failure of the tubules to reabsorb nutrients, and further additions to the list may be anticipated. One could conceive that the whole spectrum of primary nutritional diseases could be mimicked by renal wastage of specific nutrients, but it is quite possible that in some instances the inherited genes may be lethal. It would be difficult indeed to conceive of patients with genetically transmitted loss of ascorbic acid or thiamine surviving scurvy or beriberi in infancy!

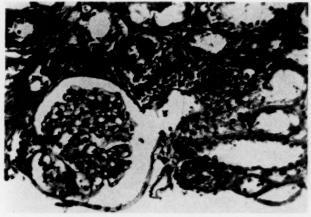


Fig. 1B. Surrounding the origin of the proximal tubule there is considerable infiltration of inflammatory cells and fibrosis. Hematoxylin and eosin, original magnification × 425.

Histologic lesions in these conditions have been studied by serial sections of renal tissue and by nephron dissection. The former method of study is often a gamble since it is difficult to demonstrate the orifice of the proximal tubule in Bowman's space, even with the most carefully cut serial sections. The latter method needs great experience for correct interpretation. Despite these drawbacks, Darmady and his colleagues were the first to demonstrate defects in proximal tubules of kidneys from patients with the Fanconi syndrome, using both technics [64], and found similar lesions in infants who had died of congenital familial nephrosis [65]. Dr. John Soothill and I [66] have observed abnormalities in tubules of nephrons dissected from renal biopsy specimens from a patient with Wilson's disease, and we have also noted abnormalities of the proximal tubules and unusual changes in the interstitial tissues surrounding it, near its insertion into Bowman's capsule. (Figs. 1A and 1B.) It was impossible to tell whether these changes were primary and caused the disease or whether they were secondary to the disease.

A third technic for investigating the minutiae of the nephron has been developed by my colleague, Dr. Sjoerd Bonting. He has described ingenious methods for studying the quantitative histochemistry of the kidney [67] which are exacting but practical, and one hopes that they will bear fruit over the next decade. Renal tissue is obtained by biopsy and is rapidly frozen in liquid nitrogen, sectioned, and lyophilized. The various parts of the nephron are accurately identified in the dehydrated sections, and they are dissected out, using microscalpels and a micro-

Table 1
DISTRIBUTION OF ALKALINE PHOSPHATASE IN THE HUMAN KIDNEY*

Structure	Healthy Individuals (6)	Adult Fanconi Syndrome (2)	Renal Glycosuria (1)	Hypophos- phatasia (1)	Lupus Nephritis (5)
Glomerulus Proximal convoluted tubules		0.4 ± 0.4 $1.2 + 1.5$	0.6 ± 0.5 2.6 ± 0.8	0.1 ± 0.1 0.2 ± 0.2†	0.74 ± 0.15
Distal convoluted tubules	2.7 ± 0.5	0.6 ± 0.9 0.6 + 0.5	1.2 ± 0.6 2.7 ± 1.4	0.2 ± 0.21	
Medullary ray	0.8 ± 0.5	0.6 ± 0.8 0.6 ± 0.8 0.5 ± 0.3		0.5 ± 0.8	
Papilla Vessels	1.3 ± 1.0 1.2 ± 0.7	0.5 ± 0.3 0.5 ± 0.1			0.7 ± 0.4

* Expressed in moles of p-nitrophenylphosphate split per kilogram (dry weight) per hour, with standard deviation. In parentheses, the number of patients studied is indicated.

† Contains distal as well as proximal convoluted tubules because it was impossible to distinguish these on the basis of morphology.

scope. The minute fragments of glomeruli or tubules, which consist of only a few cells, are handled with micromanipulators. First they are accurately weighed on gossamer threads of quartz fibers and thereafter transferred to the bottoms of minute test tubes for analysis. The activities of enzymes and the concentrations of various substances are quantitatively determined thereafter by ultramicrobiochemical technics.

Because Stowers and Dent [68] observed a decrease in stainable alkaline phosphatase in the kidney in the Fanconi syndrome, the alkaline phosphatase content of the anatomical elements of the kidneys of patients with various types of renal disease was determined. In addition, lactic dehydrogenase was studied. The kidneys

from two patients with adult Fanconi syndrome were investigated through the kindness of Drs. Robert E. Dedmon and Theodore B. Schwartz, and a patient with hypophosphatasia was studied through the kindness of Dr. Ira Rosenthal. A number of other diseases were investigated, including five patients with lupus nephritis and a carefully studied case of familial renal glycosuria.

It can be seen from Tables I and II that the levels of alkaline phosphatase activity were reduced below normal in the proximal convoluted tubules in all the patients studied, when compared with data from the nephrons of healthy individuals. This reduction was particularly marked in the patient with hypophosphatasia. On the other hand, normal lactic dehydrogenase activity was found in patients with renal glyco-

TABLE II
DISTRIBUTION OF LACTIC DEHYDROGENASE*

Structure	Healthy Individuals (8)	Adult Fanconi Syndrome (2)	Renal Glycosuria (1)	Hypophos- phatasia (1)	Lupus Nephritis (5)
Glomerulus	106 ± 28	54 ± 7	116 ± 23	213 ± 44	109 ± 37
Proximal convoluted tubules	257 ± 41	145 ± 54	299 ± 45	$357 \pm 33 \dagger$	306 ± 91
Distal convoluted tubules	256 ± 44	161 ± 53	334 ± 35		279 ± 89
Medullary ray	231 ± 25	118 ± 34	249 ± 34	375 ± 27	232 ± 58
Medulla: Outer zone		108 ± 24		326 ± 31	
Inner zone	129 ± 16	91 ± 26			
Papilla	175 ± 82	89 ± 18			
Vessel	130 ± 63	40 ± 24		203 ± 39	104 ± 73

* Expressed in moles of DPN formed per kilogram dry weight per hour (at 37°c.), with standard deviation. In parentheses, the number of patients studied is indicated.

† Contains distal as well as proximal convoluted tubules because it was impossible to distinguish these on the basis of morphology.

suria and lupus nephritis, while high levels were observed in the tubules in patients with hypophosphatasia and low levels in those with the Fanconi syndrome. The patients with the Fanconi syndrome and renal glycosuria passed large amounts of glucose in their urine, but glycosuria was never found in those with lupus nephritis and hypophosphatasia. It therefore appears difficult to attribute the abnormal urinary findings in the Fanconi syndrome and in familial renal glycosuria to a primary defect in the alkaline phosphatase activity of the proximal tubules. The depression of both alkaline phosphatase and lactic dehydrogenase activity in the Fanconi syndrome may reflect a specific effect of the disease on the tubule. However, it is not clear at this time which enzyme or group of enzymes is lacking in the Fanconi syndrome and responsible for its clinical manifestations. It also appears that neither alkaline phosphatase nor lactic dehydrogenase are key enzymes in the normal process of glucose reabsorption by the tubule. In this regard glycosuria was produced in dogs by treatment with phlorizin. Renal biopsies were performed before and after glycosuria appeared. Neither alkaline phosphatase nor lactic dehydrogenase activity was altered in the renal tubules from these animals when glycosuria was produced by the drug.

POTASSIUM DEPLETION AND THE KIDNEY

The most thoroughly investigated nutritional disease which affects the kidney is potassium depletion. Like others, we have observed reversible and permanent damage to the kidney as a result of long continued deficiency of this electrolyte. In our patients, irreversible damage has been associated with the development of chronic pyelonephritis. Four years ago my co-worker, Dr. Robert C. Muehrcke, noted that in patients with self-induced diarrhea and potassium depletion acute and chronic pyelonephritis developed during the course of their illness [69]. During the past three years he has reviewed sections of kidneys sent to him by colleagues from all over the world, from patients depleted of potassium as a result of a variety of causes. Chronic pyelonephritis was found in a significant number of these sections, particularly in those from patients with primary hyperaldosteronism [70]. This observation stimulated Dr. Muehrcke to study potassium-depleted rats, and he has been

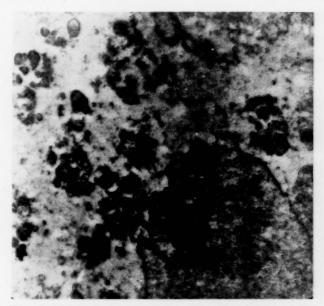


Fig. 2. Electronmicroscopic photograph of part of the collecting tubular cell from the kidney of a potassium-depleted rat. Note that the mitochondria are swollen and contain homogeneous granules. As the mitochondria undergo lysis, the granules are released into the cell. Presumably these are the eosinophilic granules previously seen with light microscopy in the kidneys of potassium-depleted rats and they indicate the primary renal lesion in potassium deficiency. (Unpublished observations of Dr. Robert C. Muehrcke.)

kind enough to allow me to mention some of his unpublished data [71]. When bacteria were injected into potassium-depleted animals a statistically significant number of them died of bacteremia as compared with control animals, and numerous scars of renal infection were found in the kidneys of those who survived the initial injection. He has also made long-term studies of depletion and repletion of potassium in hundreds of rats. Dr. Muehrcke has observed periglomerular and interstitial fibrosis associated with accumulations of inflammatory cells in the kidneys from a high proportion of his animals; and he postulates that this is the result of spontaneous infection which was not seen in the control animals. He also noted that hydronephrosis developed in 9 per cent of rats which were consuming a high intake of sodium chloride while they were on long-term depletion of potassium.

Pearse and others have considered that the locus of injury to the cell in potassium deficiency resides in the eosinophilic granules of the collecting tubule; Pearse has suspected these to be swollen and degenerate mitochondria [72]. Dr. Muehrcke has studied kidneys from potas-

sium-depleted rats with the electronmicroscope and has now clearly demonstrated that the initial damage to the kidney does indeed affect

the mitochondria. (Fig. 2.)

These studies, like others, indicate that the renal tubular cell needs adequate supplies of potassium to preserve its integrity. The physician using agents such as steroids and diuretics which deplete the body of this electrolyte must be aware of the possibilities of damaging the kidney, and of involving the organ in a secondary but permanently harmful renal infection.

REFERENCES

 RALLI, E. P., FRIEDMAN, G. J. and RUBIN, S. H. The mechanism of the excretion of vitamin C by the human kidney. J. Clin. Invest., 17: 765, 1938.

 Selkurt, E. E. The influence of glucose renal tubular reabsorption and p-aminohippuric acid tubular excretion on the simultaneous clearance of ascorbic acid. Am. J. Physiol., 142: 182, 1944.

 FOLLIS, R. H. The Pathology of Nutritional Disease. Springfield, Ill., 1948. Charles C Thomas.

 McCance, R. A. Aspects of renal function and water metabolism. In: Studies of Undernutrition, Wuppertal, 1946–1949. Sixth Medical Research Council Specialty Report Serial No. 275. London, 1951. His Majesty's Stationery Office.

5. Mollison, P. L. Observations on cases of starvation

at Belsen. Brit. M. J., 1: 4, 1946.

 Kerpel-Fronius, O., Varga, F., Kun, K. and Vönöczky, J. Relationship between circulation and kidney function in infantile dehydration and malnutrition. Acta med. Acad. sc. hung., 5: 27, 1954.

 METCOFF, J. Observations on the renal defense of body composition in children. Am. J. Clin. Nutrition, 4: 543, 1956.

 DAVIES, J. N. P. Renal lesions in Kwashiorkor. Am. J. Clin. Nutrition, 4: 539, 1956.

 Conn, J. W. and Johnson, R. D. Kaliopenic nephropathy. Am. J. Clin. Nutrition, 4: 523, 1956.

 EALES, L. Renal function in scurvy. Am. J. Clin. Nutrition, 4: 529, 1956.

- KARK, R. M. Symposium on nutrition and the kidney. Introduction. Am. J. Clin. Nutrition, 4: 463, 1956.
- 12. Kushner, D. S. Calcium and the kidney. Am. J. Clin. Nutrition, 4: 561, 1956.
- 13. Lowe, K. G. and Valtin, H. Dietary treatment in acute anuria. Am. J. Clin. Nutrition, 4: 486, 1956.
- MERRILL, A. J. Nutrition in chronic renal failure. Am. J. Clin. Nutrition, 4: 497, 1956.
- SARGENT, F. and JOHNSON, R. E. The effects of diet on renal function in healthy men. Am. J. Clin. Nutrition, 4: 466, 1956.
- SQUIRE, J. R. Nutrition and the nephrotic syndrome in adults. Am. J. Clin. Nutrition, 4: 509, 1956.
- ZIMMERMAN, H. J. Nutritional aspects of acute glomerulonephritis. Am. J. Clin. Nutrition, 4: 482, 1956
- Wenger, J., Kirsner, J. B. and Palmer, W. L. The milk-alkali syndrome. Hypercalcemia, alkalosis

- and temporary renal insufficiency during milk antacid therapy for peptic ulcer. *Am. J. Med.*, 24: 16, 1958.
- Relman, A. S. and Schwartz, W. B. The kidney in potassium depletion. Am. J. Med., 24: 764, 1958.
- MUDGE, G. H. Clinical patterns of tubular dysfunction. Am. J. Med., 24: 785, 1958.
- STANBURY, S. W. Some aspects of disordered renal tubular function. In: Advances in Internal Medicine, vol. 9, pp. 231–272. Edited by Dock, W. and Snapper, I. Chicago, 1958. Year Book Publishers, Inc.
- SMITH, H. W. The Kidney: Structure and Function in Health and Disease, p. 472. New York, 1951. Oxford University Press.
- McCarrison, R. The causation of stone in India. *Brit. M. J.*, 1: 1009, 1931.
- MENEELY, G. R., TUCKER, R. G., DARBY, W. J. and AUERBACH, S. W. Chronic sodium chloride toxicity: hypertension, renal and vascular lesions. *Ann. Int. Med.*, 39: 991, 1953.
- HARTROFT, P. M. and HARTROFT, W. S. Studies on renal juxtaglomerular cells. II. Correlation of the degree of granulation of juxtaglomerular cells with width of the zona glomerulosa of the adrenal cortex. J. Exper. Med., 102: 2, 1955.

 DAHL, L. K. Salt intake and salt need. New England J. Med., 258, 1152, 1205, 1958.

 Best, C. H. and Hartroft, W. S. Nutrition, renal lesions, and hypertension. Fed. Proc., 8: 610, 1949.

- HARTROFT, W. S. Fat emboli in glomerular capillaries of choline-deficient rats and of patients with diabetic glomerulosclerosis. Am. J. Path., 31: 381, 1955.
- GELLMAN, D. D., PIRANI, C. L., SOOTHILL, J. F., MUEHRCKE, R. C. and KARK, R. M. Diabetic nephropathy: a clinical and pathologic study based on renal biopsies. *Medicine* (In press.)
- Lind, J. A Treatise of the Scurvy, 1st ed. Edinburgh, 1753. A. Millar.
- Bachstrom, J. F. Observationes circa scorbutum, ejusque indolem, causas, signa, et curam, institutam, eorum præprimis in usum, qui Grænlandiam et Indias Orientales petunt. Lugd Bat., C. Wishof, 1734.
- DRY, T. J. Avitaminosis in natives of Rhodesia. Arch. Int. Med., 51: 679, 1933.
- Manson-Bahr, P. M. Scurvy in the tropics. In: Tropical Diseases, 8th ed. Edited by Manson-Bahr, P. New York, 1925. William Woods & Co.
- Great Britain: Mesopotamia Commission report. London, 1917. Her Majesty's Stationery Office.
- Johnson, R. E. and Kark, R. M. Feeding problems in man as related to environment. A monograph. Military Planning Division, Office of the Quartermaster General, U. S. Army, June, 1946.
- Johnson, R. E. and Kark, R. M. Environment and food intake in man. Science, 105: 378, 1947.
- KARK, R. M. and DOUPE, J. Nutrition environment and physical fitness. J. Trop. Med. & Hyg., 44: 103, 1946.
- KARK, R. M., AITON, H. F., PEASE, E. D., BEAN, W. B., HENDERSON, C. R., JOHNSON, R. E. and RICHARDSON, L. M. Tropical deterioration and nutrition. Clinical and biochemical observations in man. Medicine, 26: 1, 1947.

- BLY, C. G., JOHNSON, R. E., KARK, R. M., CONSOL-AZIO, C. F., SWAIN, H. L., LAUDENI, A., MALONEY, M. A., FIGUEROA, W. G. and IMPERIALE, L. E. Survival in the cold. U. S. Armed Forces M. J., 1: 615, 1950.
- KARK, R. M., LEWIS, J. S. and JOHNSON, R. E. Defects of permission as an emergency ration for infantry troops. War Med., 7: 345, 1945.
- KARK, R. M. Ascorbic acid in relation to cold, scurvy, ACTH and surgery. Proc. Nutrition Soc., 12: 270, 1953
- KARK, R. M., McCreary, J. F., Johnson, R. E., Melson, R. R. and Richardson, L. M. Cold weather operational trials of rations conducted at Prince Albert, Saskatchewan, Canada. Edmond Cloutier, Ottawa, 1944.
- 43. KARK, R. M., CROOME, R. R. M., CAWTHORPE, J., BELL, D. M., BRYANS, A., MACBETH, R. J., JOHN-SON, R. E., CONSOLAZIO, C. F., POULIN, J. L., TAYLOR, F. H. L. and COGSWELL, R. C. Observations on a mobile arctic force. J. Appl. Physiol., 1: 73, 1948–9.
- 44. GLICKMAN, N., KEETON, R. W., MITCHELL, H. H. and FAHNESTOCK, M. K. The tolerance of man to cold as affected by dietary modifications: high versus low intake of certain water-soluble vitamins. Am. J. Physiol., 146: 538, 1946.
- Manual for Nutrition Surveys, Interdepartmental Committee for Nutrition for National Defense, U. S. Government Printing Office, May, 1957.
- 46. Shaper, A. G. Personal communication, 1957.
- 47. Kuzuya, N. Personal communication, 1956.
- 48. Castleman, B. and Smithwick, R. H. The relation of vascular disease to the hypertensive state. Based on a study of renal biopsies from 100 hypertensive patients. J. A. M. A., 121: 1256, 1943.
- HEPTINSTALL, R. H. Renal biopsies in hypertension. Brit. Heart J., 16: 133, 1954.
- TALBOTT, J. H., CASTLEMAN, B., SMITHWICK, R. H., MELVILLE, R. S. and PECORA, L. J. Renal biopsy studies correlated with renal clearance observations in hypertensive patients treated by radical sympathectomy. J. Clin. Invest., 22: 387, 1943.
- POLLAK, V. E., PIRANI, C. L., KARK, R. M., MUEHRCKE, R. C., FREDA, V. C. and NETTLES, J. B. Reversible glomerular lesions in toxaemia of pregnancy. *Lancet*, 2: 59, 1956.
- Theobald, G. W. The toxaemias of pregnancy in women. In: Ciba Foundation Symposium, p. 23. New York, 1950. Blakiston Co.
- CRICHTON, E. C. Toxemia in South Africa. Transactions of the International Congress of Obstetricians and Gynaecologists, Dublin, 1947.

- 54. Brock, J. F. Personal communication, 1956.
- DuPlessis, I. D. The Cape Malays. Cape Town, 1944. Maskew Miller.
- Gerber, H. Traditional cookery of the Cape Malays. Cape Town, 1957. A. A. Balkema.
- WAGHSTEIN, M. and GUDAITIS, A. Detection of vitamin B₆ deficiency. Utilization of an improved method for rapid determination of xanthurenic acid in urine. Am. J. Clin. Path., 22: 652, 1952.
- AOYAMA, S. and KOLFF, W. J. Treatment of renal failure with the disposable artificial kidney. Results in fifty-two patients. Am. J. Med., 23: 565, 1957.
- 59. Gellman, D. D., Gleason, R., Pollak, V. E. and Kark, R. M. Unpublished data.
- MOORHOUSE, J. A. and KARK, R. M. Fructose and diabetes. Am. J. Med., 23: 46, 1957.
- BARON, D. N., DENT, C. E., HARRIS, H., HART, E. W. and JEPSON, J. B. Hereditary pellagra-like skin rash with temporary cerebellar ataxia, constant renal aminoaciduria, and other bizarre biochemical features. *Lancet*, 271: 421, 1956.
- FANCONI, G. Der frühinfantile nephrotisch-glykosuriche Zwergwuchs mit hypophosphatämischer Rachitis. *Jahrb. f. Kinderh.*, 147: 299, 1936.
- JACKSON, W. P. U. and LINDER, G. C. Innate functional defects of the renal tubules with particular reference to the Fanconi syndrome. *Quart. J. Med.*, 22: 133, 1953.
- CLAY, R. D., DARMADY, E. M. and HAWKINS, M. Nature of the renal lesion in Fanconi syndrome. J. Path. & Bact., 65: 551, 1953.
- DARMADY, E. M. Microdissection of the nephron in disease. Brit. M. Bull., 13: 21, 1957.
- 66. SOOTHILL, J. F. and KARK, R. M. Unpublished data.
- 67. Bonting, S. L., Pollak, V. E., Muehrcke, R. C. and Kark, R. M. Quantitative histochemistry of the nephron. *Science*, 127: 1342, 1958.
- STOWERS, J. M. and DENT, C. E. Studies on mechanism of Fanconi syndrome. Quart. J. Med., 16: 275, 1947.
- POLLAK, V. E., FLAGG, G. W., MUEHRCKE, R. C. and KARK, R. M. Potassium depletion following self-induced diarrhea and vomiting treated by prolonged psychotherapy. Clin. Res. Proc., 5: 194, 1957.
- MUEHRCKE, R. C. and MILNE, M. D. Primary hyperaldosteronism, long-standing potassium-depletion, and pyelonephritis. Clin. Res. Proc., 5: 190, 1957
- 71. MUEHRCKE, R. C. Unpublished data.
- 72. Pearse, A. G. E. and MacPherson, C. R. Renal histochemistry in potassium depletion. J. Path. & Bact., 75: 69, 1958.

Dietary Management of Diabetes Mellitus*

HERBERT POLLACK, M.D.

New York, New York

PRIOR to 1921, that is before the discovery of insulin, the physician, in treating patients with diabetes mellitus, had to devote his entire attention just to maintenance of the life of the patient. The preparations of insulin available today make possible a concept of therapy which is directed more towards establishing a normal socio-economic status.

In the pre-insulin therapies, severe limitations were placed on the nutritional adequacy of the diets recommended. Dietaries depended upon what was called "a carbohydrate-free regimen," which consisted of limited amounts of meats, eggs, cheese, and fats such as butter, olive oil, bacon and bone marrow. Certain vegetables were allowed.

The Naunyn concept of a fast day, during which only water, bouillon, tea, lemonade and wine or whiskey were taken for twenty-four hours, had many proponents. There was also the von Norden vegetable regimen. Three meals were given, each consisting of 250 gm. of thrice-cooked vegetables and salads selected from the strict list of vegetables; to these were added, in the twenty-four-hour period, four to six whole eggs, 100 gm. of butter, a little fat bacon, the yolks of three to four eggs, coffee, tea, lemonade, bouillon, and a pint of wine. Two or three such days would follow one another as indicated. Then there were the "oatmeal cures" in which 250 gm. of oatmeal or rolled oats cooked slowly for two to three hours with butter or bacon fat with eggs were given.

Allen, in 1914-1915, outlined the following principles for the management of diabetes. His first recommendation was to make the patient fast until the glycosuria ceased, and then for another twenty-four or forty-eight hours. The ketonuria was reported to decline precipitously to a level approximating what would be shown by a normal person under similar conditions of rigid diet. Allen's objective was to keep the glycosuria and ketonuria down to a minimum level. He found that simple fasting sufficed for this purpose. Alcohol was given as a food because it did not cause glycosuria and perhaps diminished ketonuria. He gave it during the fast, especially in the severe cases in which coma might reasonably be feared. He also administered sodium bicarbonate for the first few days. After the urine of the fasting patient had been sugar-free for about twenty-four hours, the

second step was undertaken, the very slow and cautious beginning of feeding, but not according to any fixed program. One requirement that he insisted upon was that in the re-feeding program the patient should remain free of both glycosuria and acidosis. The appearance of even a trace of sugar in the urine was the signal for a fast day either with or without alcohol. The fast by which the urine was made sugar-free lasted from two to ten days. Allen stated that no subsequent fast need last longer than a single day. Accordingly, in severe cases of diabetes Allen insisted that restriction of all classes of food, including protein, was necessary.

The extensive malnutrition observed in the preinsulin diabetic patient is understandable. The disease itself prevented proper utilization of carbohydrates, resulting in a secondary protein depletion, as well as the accumulation of ketone bodies from the incomplete metabolism of fats. The diets prescribed in an attempt to improve the metabolism of carbohydrates were nutritionally inadequate.

When insulin first became available the tendency was to add administration of insulin to the established therapeutic regimen. In Osler's (10th Edition, 1926, edited by McCrae) "Principles and Practice of Medicine," in the section on diabetes, it was stated that "with the use of insulin one must adhere to the same dietetic principles as previously established, i.e., the concept of under-nutrition as being important for the life of the patient." It became apparent, in the course of time, that this concept was not correct.

In that era simply keeping diabetic children alive constituted a therapeutic triumph and little if any attention was paid to their development and nutritional adequacy. There were marked similarities in the complaints of many patients with diabetes to the symptoms associated with chronic under-nutrition. Retarded growth in children, amenorrhea in females, skin infections, fatigability, inability to sustain a good work output level, asthenia, lack of sense of well-being, were some of the common ones. When under-nutrition was a life-saving treat-

^{*} From the New York University Post-Graduate School of Medicine, New York, New York.

ment, its use was justified. Obviously a malnourished living patient was better than a well fed dead one. It took many years to emancipate the physicians from this type of thinking.

The introduction of long-acting insulins, the understanding of fluid and electrolyte balance in the treatment of ketotic acidotic coma, and the use of antibiotic chemotherapy were contributing factors to the increasing longevity of the patient. The nutritional factors were obscured by the brilliant results of these achievements. The problem that evolved was the chronic invalidism of those whose lives had been extended.

Diet therapy for diabetes must include more than the control of one very obvious phase of the condition, hyperglycemia and glycosuria. In the maintenance of good health and establishment of a sense of well-being, adequacy of the nutrition of the patient is an important factor. The nutritional requirements of the individual diabetic patient must be met, and the physician should calculate his diet prescriptions accordingly.

One of the problems confronted in achieving this result is the unwillingness or inability of many elderly patients to take insulin injections daily. To placate these patients it has been a common practice to prescribe minimum diets that would not provoke glycosuria. Such diets frequently were inadequate and in some patients secondary malnutrition developed. The introduction of the oral hypoglycemic agents, which fortunately are most effective in this group of patients, has given the physician wider latitude in the prescription of diets. The optimal nutritional requirements [1] should serve as the basis for the diet prescription. It should maintain the optimum or ideal weight and supply all the essential quantities of the macro- and micronutrients. If glycosuria results from this diet, oral hypoglycemic agents should be prescribed, and if they are not effective insulin administration should be insisted upon.

A primary factor that determines the nutritional adequacy of the diet is the caloric requirement, which may be estimated from the age, sex, body size, activity and environmental conditions of the patient. Provisions for deviations from the standards must be made when indicated [2]. Thus, calculating caloric allowances on the basis of body size alone could easily penalize the undernourished or encourage the

continuation of obesity. The rate of growth and the potential growth are important additional factors. It must be remembered also that children spend about thirty hours a week, for nine months a year, in school; the other three months of the year they are much more active. There are recognizable variations from day to day in the week. One must be prepared to set up two different diets for youngsters and adolescents: The Monday through Friday schedule, when they are attending school, and the Saturday and Sunday schedule, when they are more active outdoors. In older people glycosurias are frequent on weekends because of the rest and inactivity which decrease food requirements; in younger people, on the other hand, one not infrequently sees hypoglycemic reactions on weekends.

A recent investigation of the diets consumed by diabetic patients in the United States brought several facts to light [3]. The commonest diet prescriptions for patients of all ages, in both sexes, were found to provide approximately 150 to 200 gm. of carbohydrate, from 80 to 100 gm. of protein, and from 50 to 100 gm. of fat, with a total caloric intake averaging from 1,370 to 2,100 calories daily. Such caloric allowances are barely adequate for those in the forty-five year age group. For the decade older than forty-five, they are adequate, and for the elderly they may actually supply too many calories. They are deficient for the young working adult male, and borderline for the young adult female. For children and adolescents, they are grossly deficient.

The special nutritional requirements of the diabetic pose some specific problems. Two of these are the protein and riboflavin requirements. The protein requirements of the diabetic patient may be considered to be somewhat higher than those of the non-diabetic patient. When there is uncontrolled glycosuria with or without ketosis, but especially when ketosis is present, there is usually a negative nitrogen balance, as demonstrated by nitrogen balance studies. When control is reinstituted, extra protein should be given to replenish that which has been lost during the ketotic or catabolic episode. It should be pointed out that perhaps the greatest achievement brought about by the use of the long-acting insulins has been the ability to maintain a positive nitrogen balance in the face of uncomplicated glycosurias.

Children and adolescents are the most diffi-

cult to teach to adhere to a prescribed diet but if the diets prescribed are sufficient to satisfy the hunger of the adolescent they may not have their craving for extraneous foods. Insulin dosage can be calculated with a greater degree of accuracy for a planned diet than when the individual is allowed to eat in a haphazard fashion to satisfy his inner cravings [3].

The consumption of 3,800 calories in three conventional meals can be a difficult task even for an adolescent. For these large caloric intakes, between-meal snacks must be provided. In actual practice this is indeed a happy circumstance for several reasons. The youngster or young adult can then join his contempories in their socializing at snack times. Moreover, between feedings facilitate insulin efficiency. It is virtually impossible in some cases to control glycosuria with a single injection of long-acting or intermediary-acting insulin if the meal division is in three equal, conventional units.

After the total caloric requirement has been decided upon, the proportionate amount of carbohydrates, proteins, and fats required to furnish these calories must be allocated. There are certain limitations to each category.

With respect to the carbohydrate allowance, there is an actual minimum and a theoretical maximum. The minimum is that amount less then which will result in ketonuria. In clinical practice, diets containing more than 100 gm. a day of metabolizable carbohydrates are safe in this respect. The upper limit of carbohydrate intake is controlled by the objective of therapy. If complete control of glycosuria is the aim, the total amount and type of carbohydrate must be limited. Diet prescriptions requiring from 150 to 200 gm. carbohydrates a day can be filled, using the average number and size of vegetable portions with a small portion of grain (bread or cereal), and a serving of fruit at each meal. Above this level the dependence on vegetables as a source of carbohydrates increases the actual bulk of the meal to a point beyond consumption. One must then resort to increased amounts of the more concentrated carbohydrate foods, including the fruits. This type of food increases the problem of postprandial glycosurias. With the insulins currently available a diet prescription of the order of 200 gm. of carbohydrates daily will allow for a sufficient variety of foods without undue difficulty in control of glycosuria.

The maximum amount of carbohydrate permissible is, at present, not clearly understood.

Since all food intake (especially of carbohydrate) in excess of caloric needs is deposited in the body as fat, a high carbohydrate diet can be, in effect, a high fat diet [5]. Another factor must be included in this calculation. The total amount of glucose excreted in the urine should be deducted from the carbohydrate intake when calculating the total metabolism. High carbohydrate diets provoke glycosurias with their attendant fluid and salt problems, and the percentage of fat calories burned is higher than suspected.

The latent period of activity (the time between the injection and beginning activity) for the standard insulins varies from fifteen minutes to approximately one hour, and there is a maximum duration of action of four to six hours. One is not concerned with prolonging or delaying carbohydrate availability when employing these insulins. With long-acting insulins the problem is quite different. The intermediary insulins, such as neutral protomine insulin, lente or globin, have a latent period of the order of two hours; the longer acting ones, such as protomine zinc insulin and ultra lente are of the order of four hours. The action of these insulins is prolonged from approximately eighteen to forty-eight hours.

With the long-acting insulins, the conventional food distribution into three equal meals frequently gave rise to postbreakfast glycosurias as well as to subsequent hypoglycemic reactions [6]. Attempts to increase the amount of insulin in order to control the postbreakfast glycosuria resulted in more severe hypoglycemia during the night or the following morning before breakfast. This led to proposal of various devices, such as multiple insulin injections or multiple meal schedules.

Pollack et al. showed [7] that if the availability of ingested carbohydrate could be retarded so that glucose entered the blood stream at a rate slow enough to be disposed of, the temporary glycosurias and hyperglycemias could be minimized or eliminated. Analysis of the details of the diets of the majority of patients with diabetes revealed that the standard breakfast called for at least one portion of a fruit usually consumed as fruit juice. In view of the high sugar content of fruit juices it is not surprising to find that patients using protomine zinc insulin and drinking fruit juice would have postbreakfast glycosuria.

There is insufficient information as to the rate of availability and rate of utilization of various foodstuffs and food mixtures. A few

isolated experiments have been reported showing the rate of absorption as indicated by blood sugar changes [7], and of utilization as indicated by the rate of respiratory quotient changes [8] after ingestion of specific foods and mixtures. These data demonstrate that all foods are not utilized at the same rate, but that free sugars are used rapidly and complex starches more slowly. The presence of fat in the meal greatly extends the time of metabolism of a food mixture. With regard to the breakfast of the patient using long-acting insulins it may be stated that (1) fruit juices and most fruits should not be included in the breakfast, and (2) the breakfast should be small.

Midnight and early morning reactions were the greatest deterrents, at first, to the general use of the long-acting insulins. Attempts to solve this problem led to the practice of small meals before bedtime, but this was not always feasible or satisfactory.

About 50 per cent of the protein ingested is available to the body as carbohydrate, but the carbohydrate thus formed is made available comparatively slowly. Conn and Newburgh [9] recognized this property of proteins when they suggested the use of high protein diets for the treatment of spontaneous hypoglycemia. Based on this concept, Pollack suggested [10] a third change in the standard diabetic diets, namely, the feeding of a large proportion of the protein food at the evening meal, which is taken as late as is feasible.

The possible relationship of dietary fats to the genesis of atherosclerosis has been and remains the subject of a great deal of investigation. In the last year two reports appeared which review the field in an impartial manner, one by the joint Nutrition Committee of the American Heart Association and the Society for the Study of Atherosclerosis [12], the other by the Committee on Fats of the Food and Nutrition Board of the National Research Council [13]. Both of these committees reach essentially the same conclusion, i.e., "There is not sufficient evidence available to justify recommendations of major changes in the current American Dietary."

How much and what type of fat should be incorporated into the diet and the diabetic patient? The total caloric intake, of course, is one limiting factor. The amount of fat to be prescribed must make up the difference between the calories supplied by the carbohydrates and proteins, and the total number of calories

Table 1
GRAMS AND PERCENTAGE OF CALORIES FROM FAT

Total Calories	Carbo- hydrate (Gm.)	Protein (Gm.)	Fat (Gm.)	% Fat Calories of Total Calories*
1,000	60	100	40	36
1,400	160	100	40	25.8
1,800	200	100	65	33
2,200	200	100	110	45.5
2,600	200	100	145	54
2,600	250	100	135	46
3,000	250	125	165	50†
3,400	250	150	200	53‡

* Assuming complete carbohydrate utilization and no glycosuria.

† With 50 gm. glycosuria this increases to 57 per cent. ‡ With 50 gm. glycosuria this increases to 59 per cent.

required. Table 1 illustrates the number of grams and the percentage of calories from fat. These figures are based on the fact that palatable food combinations containing 100 gm. of protein include a minimum of 40 gm. of inherent fat without the addition of butter, oil, shortening or lard. They indicate that at levels above 2,200 calories it is difficult to write diets containing less than 50 per cent of the calories from fat unless the carbohydrate intake is raised to a level that makes control of the glycosuria difficult, at least with currently available insulins. Furthermore, when glycosuria is provoked, the amount of carbohydrate metabolized is reduced and the per cent of calories from fat is higher than the calculations indicate.

Vitamin requirements in the diabetic patient are essentially the same as in the non-diabetic patient during periods of metabolic equilibria. These requirements are satisfied quite completely by most people when they have an unhampered choice of foodstuffs. A prescribed diet limits this free selection. Special care must be exercised to compensate for the nutrients contained in those foods which are allowed in limited quantities only or are eliminated altogether. In certain economic levels of society a large proportion of the daily thiamin requirement is obtained from a whole grain or from enriched breads and cereal products. Rigidly limiting the bread intake of the diabetic patient automatically eliminates a large amount of thiamin from the diet.

The accent on fruits and leafy, green vege-

tables in the diet for diabetic patients practically automatically insures the adequate intake of vitamins A and C. There is some evidence [11] of interference with normal riboflavin utilization during catabolic episodes.

One must assume that the average patient who presents himself to the physician suffers from an acute anxiety reaction when he is told that he has diabetes mellitus, and therefore must be reassured that with proper care he can largely minimize and to some extent avoid most of the complications of diabetes. The motivation of the patient must be stimulated to adhere to the regimen as prescribed. The education of the patient into the use of diet prescriptions is perhaps one of the most complicated aspects of the therapeutic problem involved. In the past, the patient has been told to eat this and not to eat that, and to select food from this list and that list, and to add them up together to make his meal pattern. The simpler we can make the dietary instruction the more easily will the patient follow the few essential restrictions which are part and parcel of most of the regimens in use today. Most leafy green vegetables theoretically contain an average of 3 per cent carbohydrate. What does it matter whether the patient takes 100 gm. of lettuce or 200 gm. of lettuce? Few patients will voluntarily eat enough lettuce at a sitting to affect their carbohydrate intake appreciably. Teach the patients to eat certain groups of foods in unrestricted quantities. This gives the patient a sense of freedom, of not having to watch every single mouthful consumed. Restrictions should be reserved for those foods which contain a carbohydrate concentration above 10 to 12 per cent. With respect to meats, very little restriction is required. The patient should be instructed to eat an average-sized portion, unless one is dealing with an obese patient.

REFERENCES

- POLLACK, H. Nutritional adequacy of the diabetic diet. *Diabetes*, 2: 497, 1953.
- POLLACK, H., CONSALAZIO, C. F. and ISAAC, G. J. Metabolic demands as a factor in weight control. J. A. M. A., 167: 216, 1958.
- POLLACK, H. Nutritional management of diabetes, p. 167. In: Proceedings of the Symposium on Diabetes—Newer Concepts of the Causes and Treatment of Diabetes Mellitus. New York, 1954. The National Vitamin Foundation.
- POLLACK, H. The altered prognosis in diabetes mellitus. Proc. A. Life Insurance M. Directors America, 39: 129, 1955.
- Jefferis, T. C., Consalazio, C. F. and Pollack, H. Studies on nutrition in the far east. VIII. Protein partition in the blood and some notes on total lipids. *Metabolism*, 5: 279, 1956.
- POLLACK, H. Dietary suggestions for the management of diabetic patients using protamine zinc insulin. J. Mt. Sinai Hosp., 10: 437, 1938.
- POLLACK, H. and DOLGER, H. Advantages of protamine zinc insulin therapy. Dietary suggestions and notes on the management of cases. *Ann. Int. Med.*, 12: 2010, 1939.
- CARPENTER, T. M. The combustion of carbohydrates in man after ingestion of common foods. J. Nurition, 19: 423, 1940.
- CONN, J. W. and Newburgh, L. H. Glycemic response to isoglucogenic quantities of protein and carbohydrate. J. Clin. Invest., 15: 665, 1936.
- POLLACK, H. and DOLGER, H. Protein as a source of carbohydrate for patients using protamine zinc insulin. Proc. Soc. Exper. Biol. & Med., 39: 242, 1938.
- POLLACK, H. and BOOKMAN, J. J. Riboflavin excretion as a function of protein metabolism in the normal catabolic and diabetic human being. J. Lab. & Clin. Med., 38: 561, 1951.
- PAGE, I. H., STARE, F. J., CORCORAN, A. C., POL-LACK, H. and WILKINSON, C. F., JR. Atherosclerosis and the fat content of the diet. *Circulation*, 16: 163, 1957.
- The role of dietary fat in human health. A report of the Food and Nutrition Board, National Academy of Sciences, National Research Council. #575, Washington, D. C., 1958.

Experimental Epidemiology of Chronic Sodium Chloride Toxicity and the Protective Effect of Potassium Chloride*

GEORGE R. MENEELY, M.D. and CON O. T. BALL

Nashville, Tennessee

The origin of the human custom of adding sodium chloride to food is still hidden in pre-history. Throughout the historical period of man, salt is found in use in almost all civilizations. Concurrently there have always been speculations that extra salt was not needed, even some suspicions it might be harmful. The rich and varied literature on salt and humankind has been scanned by others and by us [1–10]. Only in the present century did evidence begin to accumulate for a relation between salt and hypertension in man [11–18]. Research by Selye [19], Sapirstein [20], Fukuda [21] and others showed by animal experiment the hypertensigenic action of sodium chloride.

Thompson [22] has complained of a lack of candor among scientists to tell what really was the inception of some worthwhile line of research, suggesting instead of the portentous "In view of the recent evidence concerning . . . " the more factual " . . . we happened to be fooling around one day when . . . " Real efforts at candor, however, are likely to be awkward or embarrassing or both, and suffer from the added demerit that an excess of candor usually does, of leaning backward from the facts as far as specious reason may lean into them. At the outset of these studies, early in 1951, Robert G. Tucker had come to join William J. Darby and us for the purpose of engaging in medical research. For reasons probably not even known to himself, one of us developed at that time a curiosity about the long term effect of added sodium chloride in the diet. A search of the literature revealed an immense number of publications pertaining to salt and concomitant variables, very little about salt alone. The fine

work of Sapirstein [20] had not yet come to our attention and we failed also to find the important paper of Fukuda with Selye [21].

We designed an experiment intended to test increased sodium chloride as the sole variable in a purified diet. The rats immediately added a variable of their own by altering their fluid intake according to the salt intake, a phenomenon reported in Pliny's Natural History somewhat earlier. We had in mind the possibility that excess salt might manifest itself as a source of degenerative disease, nature unspecified. Our minds were open, even perhaps blank.

It is the purpose of this article to review in one place what we have found so far, most of which we have reported piecemeal elsewhere [23–34]. Before doing so it is appropriate to relate the participation of those who worked in these studies. Stewart Auerbach joined the investigation and throughout the early years dealt with the microscopical-anatomical phases of the study. Later, Ernest Goodpasture devoted a period of intensive study to the high salt eating animals of experiment 1. His report has been drawn upon for some comments later in this paper but the main body of his findings are not yet published. Ross C. Kory developed the technic for electrocardiography employed, established criteria for interpretation of the rat electrocardiograms and studied the entire colony. Further electrocardiographic investigations were conducted by Thomas M. Blake and he participated in the pathological studies. When Robert Tucker moved on from the group, Janet Lemley-Stone assumed general charge of the animal colony and the biochemical and radioisotope phases of the investigation.

^{*}From the Departments of Medicine and Preventive Medicine and Public Health, Vanderbilt University School of Medicine, Nashville, Tennessee. The work reviewed in this report was performed in the Research Laboratory and the Radioisotope Service of Thayer Veterans Administration Hospital and the laboratories of Vanderbilt University School of Medicine. It was supported in part by the Life Insurance Medical Research Fund and the National Institutes of Health (H-1816).

From its inception, John B. Youmans stood as an interested adviser and observer. Beginning in 1953 he became an active participant, devoting himself most especially to the experiment in dogs. While some preliminary observations from the dog colony have been reported, it is intended to restrict the presentation here to a review of the findings to life span studies in 825 rats.

EXPERIMENTAL PLAN

Young male Sprague-Dawley rats, weight about 115 gm., were used throughout except for Experiment IV in which female rats were the subjects and Experiment III in which some "elderly" rats were used. The animals were kept in suspended cages in temperature and humidity controlled quarters with free access to the particular diet provided and with demineralized or distilled water ad libitum. The basic ration of casein, sucrose and hydrogenated vegetable fat with a vitamin premix and a mineral mixture similar to the Hubbell, Mendel and Wakeman [35] mixture, but lacking sodium chloride, was adjusted to various salt levels by the addition of powdered sodium chloride which was then intimately mixed in a mechanical food mill. The animals were weighed frequently and the cages and stands were kept scrupulously clean. The copious urine flow was dealt with by liberal use of cedar sawdust and shavings on pullthrough cage rack papers. Blood pressures were measured by the photoelectric tensometer method of

TABLE I BASIC RATION

Ration	%
Casein, vitamin test	25.1
Cane sugar	51.8
Shortening, all vegetable (Crisco)	20.0
Mineral mixture	2.9*
Vitamins	0.2

^{* 0.01} per cent NaCl by analysis.

Kersten et al. [36]. Other methods employed are documented in the individual reports already referred to.

SUMMARY OF EXPERIMENTS I THROUGH VIII

Experiment I began on November 7, 1951. One hundred ninety-one rats were divided into six groups of thirty each and one group of eleven. The latter small group ate the basic ration without added sodium chloride which, by analysis, contained only 0.01 per cent sodium chloride. (Table I.) The most significant observation in this small group was that 0.01 per cent sodium chloride is suboptimal as evidenced by anorexia, diminished growth and decreased survival rate. (Fig. 1.) For our purposes here, no further

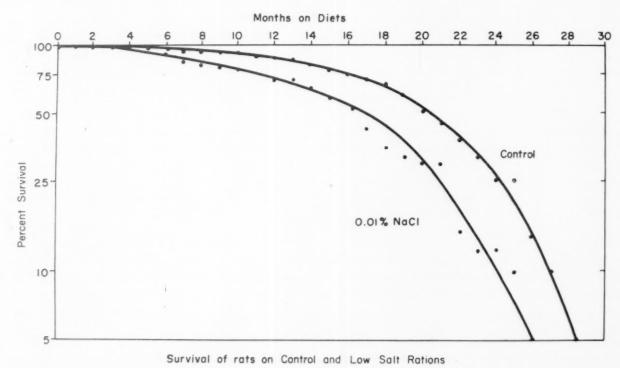


Fig. 1. Experiments 1 and 11. 43 rats given 0.01 per cent NaCl (low salt); 57 rats 0.15 per cent NaCl (control).

TABLE II
PER CENT SODIUM CHLORIDE IN RATIONS

Ration Group	% NaC
ıı (Control)	0.15
ш	2.8
ıv	5.6
v	7.0
vi	8.4
VII	9.8

Table IV
MEAN RATION CONSUMPTION FIRST FIVE WEEKS

Ration	% NaCl	Gm./Rat/Day
ıı (Control)	0.15	13.1
m	2.8	13.0
IV	5.6	13.1
V	7.0	13.9
VI	8.4	14.1
VII	9.8	13.6

attention will be given these low salt eating animals.

The levels of sodium chloride fed are shown in Table II while Table III shows the relation of these rations to the human diet. The significant observations derived from groups II and VII of experiment I were manifold. The diet consumption of those animals eating higher levels of salt was slightly greater (Table 1V), possibly an effort to stay isocaloric. Water consumption was essentially proportional to dietary sodium chloride up to 8.4 per cent, but above this no further increase in fluid intake occurred. Urine formation of course paralleled the fluid intake. Growth was inversely affected by salt intake, each increment of salt producing a small but consistent decrement in weight gain. (Table v.) This impaired growth persisted throughout life. (Table vi.)

From the second to the sixth month of this experiment and at the same time and at the same per cent incidence (15 per cent) in all similar experiments there occurred sporadically among rats eating 7.0 per cent sodium chloride and above, a curious nephrosis-like syndrome. Figure 2 shows such an animal. The onset of edema was abrupt and it was massive. (Fig. 3.) The other important features of this syndrome were hypertension in most animals, anemia,

TABLE III
COMPOSITION OF HUMAN DIET

Gm./Day	Calories/Day
100	400
100	900
300	1,200
500	2,500
14	
	100 100 300

Table v

Mean body weight in grams after twenty weeks on regimen—initial weights 116 to 121 gm.

Ration	% NaCl	Weight (gm.)		
Kation		Mean	S.D.	
II (Control)	0.15	472	39	
ш	2.8	449	34	
IV	5.6	432	26	
V	7.0	424	36	
VI	8.4	413	35	
VII	9.8	395	28	

pronounced lipemia, severe hypoproteinemia, and azotemia was invariable. All animals victim to this disorder died, usually in the edematous phase, less often after loss of edema and development of cachexia as in the illustrated case. All these animals showed severe arteriolar disease, the nature of which will be described in the summary of the microscopical-anatomical observations.

It was early noted that hypertension was oc-

TABLE VI LENGTH AT DEATH

Ration	% NaCl	Length (cm.)			
Ration	% NaCi	Mean	SEM*		
11	0.15	26.5	0.4		
III	2.8	26.0	0.3		
IV	5.6	25.9	0.2		
v	7.0	25.7	0.3		
VI	8.4	25.3	0.2		
VII	9.8	24.8	0.2		

^{*} Standard error of the mean.

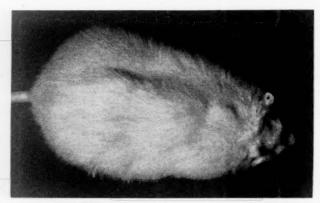


Fig. 2. Edematous rat. Death at eight weeks. Weight 440 gm., 8.4 per cent NaCl.

curring among the high salt eating rats. Observations of the blood pressure in the colony of experiment I were consistent and reproducible by about the ninth month. At this time it was found that significant hypertension was present at all levels of increased dietary sodium chloride, namely from 2.8 to 9.8 per cent. Figure 4 shows the individual values at that time and Figure 5 shows the mean and standard error of the mean for all the groups. It was evident from these data

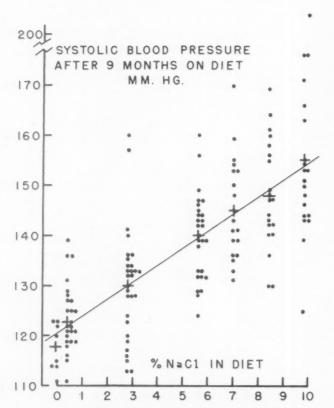


Fig. 4. Individual blood pressure values. Each point represents the average of four to six readings.

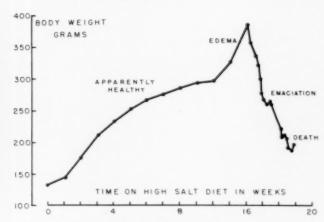


Fig. 3. Weight curve of rat dying at nineteen weeks after loss of edema, 9.8 per cent NaCl.

that the elevation in blood pressure was generally proportional to the amount of salt in the diet but also there was quite a marked degree of individual variation. Later, analysis of the blood pressure data for the whole colony and the entire life span showed that individual rats tended strongly to maintain their place in their own array. Those severely hypertensive in any one group at any one time were the same as those severely hypertensive at a later date. Those at levels of blood pressure well below the mean for their group were also later those showing the lower levels of pressure. It was evident on further analysis that at high levels of high salt feeding the blood pressure rose rapidly to high levels while at intermediate and lower levels of high salt feeding, the blood pressure rose less rapidly to intermediate hypertensive levels. Blood pressure correlated inversely with the weight of the animals. (Figs. 6A and 6B.)

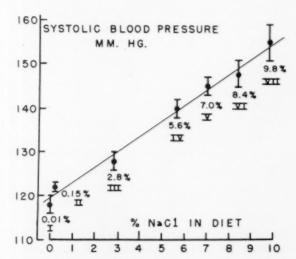


Fig. 5. Mean blood pressure values at nine months.

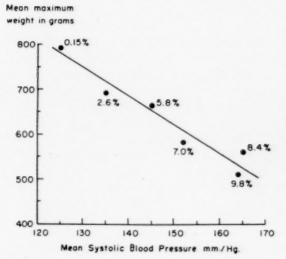


Fig. 6A. Mean group blood pressures (SEM \pm 5 to 8 mm. Hg) at mean maximum weight (SEM 5 to 10 gm.).

At about the nineteenth month of experiment 1 electrocardiograms were obtained from all surviving animals. The incidence of electrocardiographic abnormalities were directly proportional to the amount of salt in the diet. Further, the specific abnormalities observed were closely similar to those of human hypertensive subjects, namely: a high incidence of T wave abnormality; S-T segment abnormality; left axis deviation; left ventricular strain pattern and prolonged duration of the QRS complex. Only a low incidence of arrhythmia and P-R interval abnormality occurred. (Table vII.) Analysis of the blood pressure data showed that those rats exhibiting the higher levels of blood pressure early in life were those who supplied the highest incidence of electrocardiographic abnormality late in life, just as they were the ones whose pressures were at the highest levels later in life.

Table VII
INCIDENCE OF ABNORMAL ELECTROCARDIOGRAMS
AT NINETEEN MONTHS

	% Dietary NaCl					
Abnormality	0.15	2.8	5.6	7.0	8.4	9.8
T wave		15		20	30	50
ST segment	5	4		20	45	20
Left axis deviation	3	18	15	30	50	55
Left ventricular strain		3		10	45	50
Arrhythmia						20
Prolonged P-R interval.		3	5		5	25
QRS duration			16	15	35	25

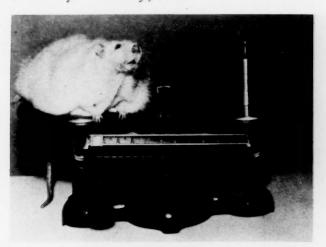


Fig. 6B. "Winston," a 1 kg. eater of 0.15 per cent NaCl and too many calories, seen here in his late middle age (twenty months) is massively obese and manifestly content. His blood pressure is perfectly normal (122 mm. Hg) and his cholesterol reassuringly low (178 mg. per 100 ml. serum).

Hyperlipemia among the nephrotic animals was not the only evidence of disturbed lipid metabolism. As will be seen, lipid deposits occurred in arterioles throughout the body and in the renal parenchyma. The serum cholesterol levels tended to increase with increasing dietary sodium chloride (Table VIII), but more striking was the correlation ($r = +0.54 \pm 0.12$) between serum cholesterol and the observed level of the blood pressure. (Fig. 7.) Elevated cholesterol did not occur in normotensive animals, although not all hypertensive animals were hypercholesterolemic. The second quadrant of Figure 7 is seen to be empty.

Survival rate data were obtained from experiment 1. Dramatic differences in survival were observed between the groups eating various levels of salt, a sharp curtailment of survival

Table VIII
RELATION OF SERUM CHOLESTEROL TO DIETARY SALT AFTER
EIGHTEEN TO TWENTY-ONE MONTHS ON REGIMEN

Mean Serum Cholesterol (mg. %)	% NaCl				
178	0.15 (Control)				
185	2.8				
182	5.6				
240	7.0				
200	8.4				
250	9.8				

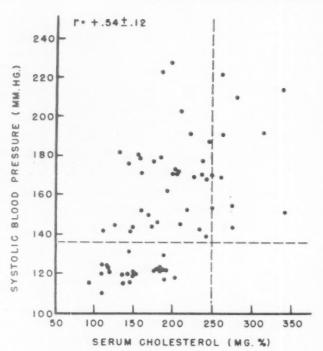


Fig. 7. Individual serum cholesterol values at eight months.

with increasing dietary sodium chloride being the leading feature of the observations. Subsequent experiments replicated parts of experiment 1 and the new data gratifyingly reproduced the earlier studies. Discussion of the observations on survival as influenced by the various levels of sodium chloride intake is therefore deferred until subsequent experiments are reviewed, shortly, in order that all available data may be pooled. The same is the case with the observations made at autopsy and upon microscopical-anatomical study because again the results were so closely similar in similar groups.

Experiment II began on November 4, 1952. It was designed to replicate parts of experiment 1 which was still in progress, but more important, it explored very high levels of high salt feeding (14 and 21 per cent sodium chloride), and it explored the gap between the 0.15 per cent and 2.8 per cent sodium chloride rations of experiment I by adding 1.1 and 2.0 per cent sodium chloride rations. Observations of blood pressure and survival showed no statistically significant difference in either of these parameters between rats eating 0.15 per cent sodium chloride and those eating 1.1 or 2.0 per cent sodium chloride, but in both these latter groups growth was improved over that of the 0.15 per cent rats. From these observations it was concluded that sodium chloride intake from 0.15 per cent to 2.0

per cent represents about the optimal, with growth data slightly favoring the 1.1 per cent to 2.0 per cent level. In subsequent studies for all purposes other than evaluating growth, data from rats eating the basic ration with from 0.15 to 2.0 per cent sodium chloride added are pooled as control values. The 14 and 21 per cent sodium chloride rations were lethal early as will be seen in the discussion of survival to follow.

Experiment III was small, for the purpose of testing the effect of increased sodium chloride starting late in the life of the animal. Through the courtesy of Dr. Kenneth Kohlstaadt of Eli Lilly and Co., a colony of twenty-six elderly rats (nearly two years old) who had lived on chow diet was made available. On December 2, 1953, they were placed on purified diets containing 1.1 per cent (control), 5.6 and 9.8 per cent sodium chloride. The rats eating the 5.6 and 9.8 per cent diets did become hypertensive but it is of interest to note that the levels of elevated blood pressure attained were always less than was the case with young rats who ate the same ration. From this it may be concluded that the hypertensigenic action of increased sodium chloride affects old as well as young animals, but as is the case with other hypertensigenic regimens the older animals are not as vulnerable as the vounger.

Experiment IV consisted of forty-eight female rats in four groups of twelve for the purpose of comparing the effects of dietary sodium chloride increases in the female with those seen in the male. Further, it explored the question whether or not an ordinary commercial rat chow diet with added salt would produce the same blood pressure changes as did the purified diet. The level of blood pressure in female rats eating the control diet (in this case, 0.15 per cent sodium chloride) was not significantly different from that of the control male rats, being 124.2 \pm 2.1 mm. Hg at the tenth month. During the same interval systolic blood pressures of 139.3 ± 0.4 and 149.8 ± 1.3 mm. Hg, respectively developed in the female rats on the purified diets containing 5.6 and 9.8 per cent sodium chloride. These are frankly hypertensive levels but the amount of the elevation of the blood pressure is less than that observed in male rats after similar periods on the same diets. Rats seem thus to share with man a proclivity for hypertension to be milder in the female. In those rats eating the commercial chow diet with 5.6 per cent sodium chloride systolic blood pressure of 140.1

TABLE IX
SUMMARY OF EXPERIMENTS I THROUGH VIII

NaCl (%)	KCl (%)	(M)	(M)	(M, aged)	(F)	(M)	(M)	(M)	(M)	Total
0.01	0.66	11	30							41
0.15	0.66	30	27		12		20			89
1.1	0.66		28	9		13	20		15	85
2.0	0.66		28				20			48
2.8	0.66	30 .					19			49
5.6	0.66	30		8	12	7		30		87
7.0	0.66	30								30
8.4	0.66	30				7		30		67
9.8	0.66	30	30	9	12			30	15	126
14.0	0.66		30							30
21.0	0.66		30							30
5.6					12			***		12
and chow)				1						
5.6	2.89					13		30		43
8.4	4.68					13		30		43
9.8	5.56							30	15	45
Total		191	203	26	48	53	79	180	45	825

 \pm 1.2 mm. Hg developed while, as noted previously, in those on a purified diet with the same sodium chloride content pressures of 139.3 \pm 0.4 mm. Hg developed. It is obvious that the hypertensigenic effect of the added sodium chloride is identical whether the basic ration is a purified one or ordinary commercial chow.

Experiment VI began June 15, 1955, with fifty-nine rats eating 0.2, 1.1, 2.0 and 2.8 per cent sodium chloride. It further replicated experiments I and II with regard to the "optimal" level of salt intake.

Experiment v, started on November 10, 1953, was a pilot run of fifty-three rats eating diets which contained added sodium chloride and added potassium chloride as well as concurrent negative and positive controls. As soon as it was evident that important differences in survival were resulting from the added potassium chloride, a larger run of animals was initiated on June 15, 1955, experiment VII, with 180 rats.

Further replication of dietary high sodium chloride with extra potassium chloride was the aim of experiment viii which began on November 21, 1956, with forty-five rats. Careful analysis of the data from experiments v, vii and viii showed such consistent behavior in rats on these diets that all these data concerning the effect of added potassium on the effects of high dietary

sodium chloride could be pooled. As already indicated, control data from experiments I, II, III and VI can also be pooled with the concurrent negative controls of experiments V and VIII. The numbers and categories available for analysis in this connection are shown in Table IX.

ANATOMICAL FINDINGS IN RATS EATING INCREASED SODIUM CHLORIDE

The autopsy data and tissue microscopical examination are most complete for experiments I and II. An immense amount of work remains to be done on this score, but the preliminary results are clear-cut and consistent. As earlier remarked, the stature of the animals observed at the time of death showed a small decrement for each increment of added dietary sodium chloride. (Table vi.) Organ weights showed consistent behavior for heart and kidney, less so for the adrenals. (Table x.) Heart weight and kidney weight increased as the level of dietary sodium chloride increased. Adrenal weight increased at high levels of high salt feeding (9.8 per cent) but below this level there is only a slight trend without statistical significance.

The basic finding on microscopic examination of the tissues is a disorder primarily affecting the arterioles and small arteries, seen most strikingly in the kidney and the parenchymatous

TABLE X
HEART, KIDNEY AND ADRENAL WEIGHTS

% NaCl		art /kg.)	Kid (gm.	ney /kg.)	Adrenal (mg./kg.)	
	Mean	SEM	Mean	SEM	Mean	SEM
0.15	2.9	0.3	7.5	1.0	158	9
2.8	3.5	0.4	8.8	1.1	165	7
5.6	3.9	0.5	9.5	1.0	163	8
7.0	4.1	0.3	12.1	1.2	168	7
8.4	4.4	0.6	10.5	0.9	173	10
9.8	5.5	0.5	13.5	1.3	203	7

organs. The glomeruli are enlarged but almost bloodless due to swelling and vacuolation of both endothelium and epithelium with large amounts of sudanophilic lipid. The tubules are dilated and the epithelium is hyperplastic and swollen with lipid and hyaline droplets. The small arteries and arterioles show fatty degeneration of muscle cells and often undergo smudgy eosinophilic necrosis. Similar arteriolar lesions are found in other viscera, especially the pancreas and testes.

The ground plan of the anatomical changes

was the same whatever the clinical picture may have been but there was marked variation in the extent of the lesions and, in the case of the kidney, the proportionate number of structural elements involved. Thus in animals which succumbed to the nephrotic syndrome and those exhibiting a "malignant" clinical course of severe hypertension the renal parenchyma was the site of a devastating process resembling that seen in necrotizing arteriolar disease in human malignant hypertension. In the milder clinical forms of hypertension seen in rats eating lower levels of high salt there were arteriolar lesions ranging from mild and sparse to moderately severe and widely distributed. At high levels of high salt feeding (9.8 per cent) Ernest Goodpasture found that there was an invariable association of severe arteriolar disease in the testis with a severe renal vascular lesion. He pointed out this might serve as a method of study of the pathogenesis of the lesion, since the testis is available for biopsy.

SURVIVAL OF RATS EATING VARIOUS LEVELS OF SODIUM CHLORIDE

As earlier mentioned, it was shown by statistical analysis that survival data from a number of the experiments could be pooled. The impaired

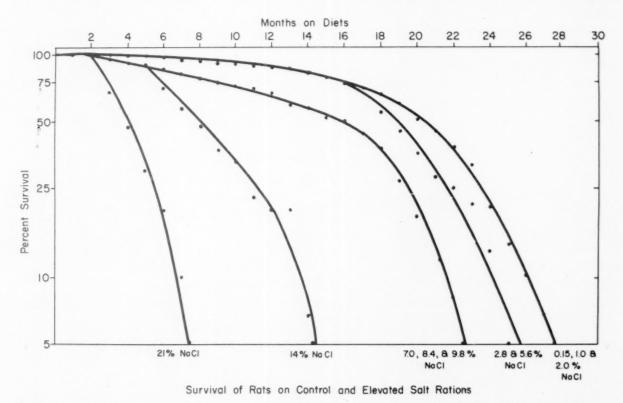


Fig. 8. Six hundred seventy-nine young male rats maintained throughout life on 0.15 to 21.0 per cent NaCl.

survival on a low sodium chloride intake has already been discussed. The polled survival data are shown by means of a semi-logarithmic graph of per cent survival against time on the particular diet. (Fig. 8.) Such curves have the property that slope of the line indicates the mortality rate and segments of such curves which are parallel thus indicate identical rates. Pooled survival data for the levels of 0.15, 1.1 and 2.0 per cent sodium chloride in the diet provide the "control" survival curve. There was no significant difference in the survival of rats taking 2.8 and 5.6 per cent sodium chloride, and these groups taken together do not exhibit an excessive mortality rate compared with controls until the nineteenth month. Thereafter they died at an accelerated rate. This seems especially important, for if the experiments had been pursued for only a year and a half this difference would not have been observed, yet the acceleration of mortality was such that the median duration of life was shortened from a control level of twenty-three months to nineteen months. If ten days for a rat equals a year for man, this is equivalent to a twelve year diminution in the median duration of life, surely a significant datum. The rats eating 2.8 and 5.6 per cent sodium chloride run a clinical course which mirrors faithfully the course of "benign" human hypertension, namely, there is little to be found out of the way among such animals except the moderate elevation of blood pressure until the nineteenth month (equivalent to the midfifties for man) after which time they begin to die more rapidly than their fellows eating "normal" amounts of salt. Even at autopsy there is little to see relevant to hypertension except in those whose blood pressure ranged up to the higher levels.

Survival among the rats eating 7.0, 8.4, and 9.8 per cent sodium chloride again was not different as among themselves, but it was significantly less than that of controls by the third month. From this time on, at first gradually and later more precipitately, mortality among these rats accelerated. The median duration of life was shortened to sixteen months. The 14 per cent and the 21 per cent sodium chloride diets were rapidly lethal, 50 per cent of animals dying by the eighth and the fourth month, respectively. From the control animals on through those eating higher and higher levels of salt, there is seen a spectrum of clinical manifestations ranging from the heterogenous common causes of death

of colony rats, bronchopneumonia and other diffuse and focal infections, to those syndromes more definitely associated with vascular disease and hypertension, namely chronic congestive heart failure, renal failure and cerebral vascular accident. Acceleration of mortality manifests itself less clearly in the nature of the terminal illness than in the time of onset of the final phase.

EFFECT OF ADDED POTASSIUM CHLORIDE IN DIETS HIGH IN SODIUM CHLORIDE

Elsewhere we have discussed at length the reasons which suggest an association between dietary sodium and potassium. In brief, it was found over one hundred years ago that a real difference between an herbivorous and a carnivorous diet lies in the much higher potassium content of the former. The sodium level of one is hardly different from that of the other. Since that time, immense amounts of speculation and a lesser amount of research has been devoted to this thesis. Possibly the concept that herbivores must go to salt licks while the carnivores need not because of the higher potassium intake of the herbivores may be specious. It is certainly true that some "salt licks" have little sodium chloride in them and the whole affair is in heated dispute among those who study these matters [5,6,37-40]. Whatever may be the real case, some striking human data are available. Much of this has been referred to in earlier presentations but it certainly is worthwhile to call attention again to the data of Priddle [17] and McQuarrie [18]. It is clear enough that in some instances of hypertension in man salt restriction alone may lower the pressure, that extra potassium may lower it further and, in a few well documented studies, extra potassium has lowered pressure from hypertensive to normal levels without the limiting of dietary sodium chloride. On the other hand, there is no general agreement as to the role of salt restriction and/or potassium administration in human hypertension. The data from the rats eating excess sodium chloride and extra potassium chloride may be helpful in this connection because, in the high salt eating rat, there are at least two different kinds of hypertension and two different ways in which extra potassium chloride alters the situation.

In a carefully tended colony of rats, survival is one of the most sensitive criteria for evaluation of noxious effects. It is a "complete" criterion in the sense that survival of an animal is a summation of all the influences, both favorable and

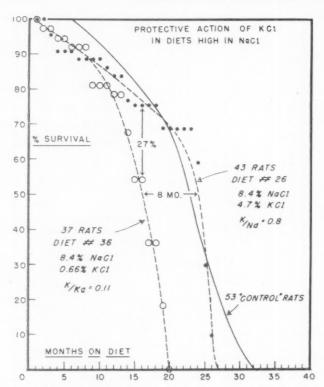


Fig. 9. Survival of rats eating 8.4 per cent NaCl with and without added KCl.

adverse, which act on it during its life. When sufficient numbers of animals are observed under standard conditions, individual variations in response are randomized and trends in survival become apparent. The survival criterion proved most useful in assessing the long-term noxious effects of added sodium chloride and, subsequently, the protective effects of potassium chloride added to diets high in sodium chloride.

It is not practical to raise the potassium to sodium ratio to values comparable to that of "normal" diets when there is much added sodium chloride in the ration, for the total amount of sodium plus potassium salt would become a very large fraction of the ration. It was therefore decided to raise it from the level of 0.1 to 0.8 per cent. In the case of the 5.6 per cent sodium chloride diet, 2.9 per cent of potassium chloride was added, while in the 8.4 per cent diet, 4.7 per cent of potassium chloride was added. The effect of these additions was to produce a striking increase in survival in each case. (Fig. 9.) The median duration of life of rats eating 8.4 per cent sodium chloride added to the basic ration (0.66 per cent in potassium chloride, K: Na ratio 0.11) was sixteen months. The median duration of life of rats eating 8.4 per cent sodium chloride and 4.7 per cent

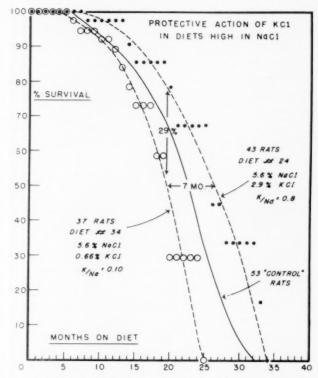


Fig. 10. Survival of rats eating 5.6 per cent NaCl with and without added KCl.

potassium chloride (K:Na ratio 0.8) was twenty-four months, approximately the same as that of the control animals (0.15 and 1.1 per cent sodium chloride, 0.66 per cent potassium chloride, K: Na ratio 6.0 and 0.8, respectively). The increase in median duration of life was eight months. If ten days for a rat equals one year for man, this represents an increase equivalent to twenty-four years for man. The effect upon survival of adding 2.9 per cent potassium chloride to the 5.6 per cent sodium chloride ration was equally great: the median duration of life was increased seven months, equivalent to approximately twenty-one years for man. (Fig. 10.) Animals receiving extra potassium chloride in the 5.6 per cent sodium chloride ration outlived the controls by several months, suggesting that the control diet is suboptimal in potassium, sodium or both.

The blood pressure data for these animals are of great interest. A moderate increase in sodium chloride (5.6 per cent) produces, as earlier shown, a moderate hypertension. Added potassium chloride does not alter this effect (Fig. 11) despite its dramatic effect upon survival. On the other hand, while high levels of increased sodium chloride feeding (8.4 per cent) produce high levels of hypertension, the effect of added potas-

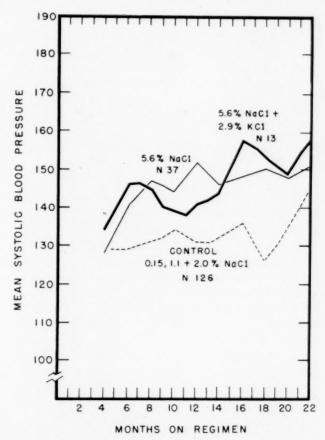


Fig. 11. Blood pressures in pilot experiment, 5.6 per cent NaCl with added KCl.

sium chloride is to moderate the hypertension to an intermediate level, about the same as seen at 5.6 per cent sodium chloride feeding with or without extra potassium chloride. (Fig. 12.) These are the two important effects of extra potassium chloride in diets high in sodium chloride evident from these data: survival is greatly increased at both levels but blood pressure is affected only at the high level of sodium chloride feeding, and then the effect is only to moderate it to intermediate levels. By the same token, there are evidently at least two kinds of hypertension in animals eating excess sodium chloride: (1) a moderate hypertension associated with moderately high levels of increased sodium chloride intake and which is not ameliorated by increased potassium feeding, and (2) a high hypertension associated with high levels of sodium chloride feeding which is moderated to intermediate levels by extra potassium chloride.

These are not the only evidences for two different kinds of hypertension and two different effects of extra potassium chloride in diets high in

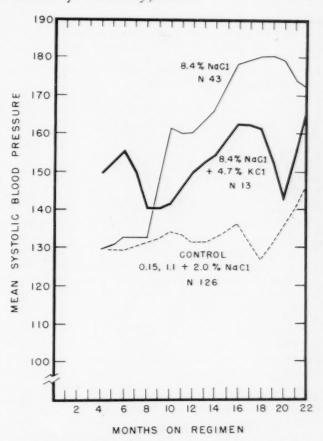


Fig. 12. Blood pressures in pilot experiment, 8.4 per cent NaCl with added KCl.

sodium chloride. Total body sodium, normally about 33.6 mEq./kg. of rat, is not increased above this level by diets containing 5.6 per cent sodium chloride, nor is it significantly altered when 2.9 per cent potassium chloride is added to this ration. (Table xI.) On the other hand, high levels of high sodium chloride feeding

Table Xi*

Total exchangeable sodium (mEq./kg.) after eight to ten months on regimen

Diet	Total Exchangeable Na (mEq./kg.) Mean
0.15 and 1.1% (Control)	33.6
5.6% NaCl	34.1
5.6% NaCl plus 2.9% KCl	34.8
8.4% NaCl	39.4
8.4% NaCl plus 4.7% KCl	35.6
9.8% NaCl	43.4
9.8% NaCl plus 5.6% KCl	35.4

^{*} Analyses of sodium and potassium were performed with the Coleman Instrument Co. Inc. flame photometer.

Table XII*
TOTAL BODY SODIUM AND TOTAL BODY POTASSIUM

Diet	Mean Body Weight (mEq./kg.					
Diet	Na	K				
Control	54	90				
High Na	58	97				
High Na plus high K.	50	108				

* Analyses of sodium and potassium were performed with the Coleman Instrument Co. Inc. flame photometer.

(8.4 and 9.8 per cent) do result in increased total exchangeable sodium (16.8 and 28.5 per cent excess, respectively). When potassium chloride is added to these rations to bring the potassium to sodium ratio to 0.8, this accumulation of extra body sodium does not occur. There is no evident causal relation other than the association, but one is tempted to link the occurrence of high hypertension with the accumulation of extra body sodium and the moderating effect of extra potassium chloride to the concurrent prevention of accumulated sodium excess. Whatever may be the correct interpretation, the complexity of the sodium to potassium relationship in the rat should be ample warrant that the situation in man will not be simple. As a working hypothesis these data suggest that we should attempt to recognize at least five categories of man: (1) those with "optimal" sodium and potassium intake; (2) those with moderately increased sodium intake and low potassium intake; (3) those with moderately increased sodium intake and increased potassium intake; (4) those with high sodium chloride intake and low potassium intake; and (5) those with high sodium chloride intake and increased potassium intake. In each of these five the electrolyte status and the response to therapeutic maneuvers should be different and, perhaps, recognizable.

In this connection some help may be had from measures of total body potassium as well. When extra sodium chloride is fed, not only does the total exchangeable sodium tend upwards but so too does the potassium. (Table XII.) This is contrary to what one might expect, a sort of reverse von Bunge effect. When high potassium chloride is fed in diets high in sodium chloride, not only is the increase in total body sodium limited as already described, but, as might be expected, total body potassium is greatly increased.

CONCLUSION

Koch's postulates can be revisited with profit [41] but cannot be fulfilled for metabolic diseases: there is no comparable touchstone for physiological states. Nevertheless, sodium chloride is present and discoverable in every form of hypertension. It is obtainable in pure form. When administered as the sole (?) variable in the diet, it reproduces the disease in susceptible animals. It would be absurd to try further to bend Koch's law to this unintended purpose.

Dahl's [42,43] observations in human subjects bear out the relation of salt to hypertension in man. More recently, the efficiency of the desalting diuretic, chlorothiazide, in the management of hypertension supports the same thesis. One wonders where the potassium chloride data fit the human picture. Does extra potassium have a role in the human dietary or only so if sodium chloride is consumed to excess? Does extra sodium chloride serve any meritorious purpose or is it really only a habit-forming noxious agent? These and many other questions are unanswered. As one of us has earlier remarked, salt is rough on rats. There may, too, have been some potash in the fountain of youth.

Acknowledgment: Walter R. Early, Medical Biology Technician, Thayer Veterans Administration Hospital and Thelma G. Turner, Technician, Nutrition Division, Vanderbilt University School of Medicine, meticulously supervised animal care, mixed diets, made weight and blood pressure measurements, and recorded data.

ADDENDUM

It is difficult to do something entirely novel in medicine. Emily Townsend Vermeule, the scholar of antiquity, has drawn our attention to the report of Kramer and Levey [44] on the oldest medical text in man's recorded history, a Sumerian physician's notebook of prescriptions. In this 4,000 year old baked clay tablet is a recommendation to include potassium nitrate in a number of the medicaments described. We, however, used the chloride.

REFERENCES

- Dahl, L. K. Medical progress. Salt intake and salt need. New England J. Med., 258: 1152, 1205, 1958.
- ESKEW, G. L. Salt, the Fifth Element. Chicago, 1948.
 J. G. Ferguson.
- Hughes, E. Studies in Administration and Finance. Manchester, 1934. University of Manchester

- 4. Jones, E. Essays in Applied Psychoanalysis, vol. 2. London, 1951. Hogarth Press.
- 5. KAUNITZ, H. Causes and consequences of salt con-
- sumption. Nature, London, 178: 1141, 1956.

 6. McCance, R. A. Medical problems in mineral metabolism (Goulstonian lectures). Lancet, 1: 643, 704, 765, 823, 1936.
- 7. Meneely, G. R. (Editorial). Salt. Am. J. Med., 16: 1,
- 8. Smith, J. R. Salt. Nutrition Rev., 11: 33, 1953.
- 9. Sмітн, W. R. Salt: ancient history and religious symbolism. In: Encyclopedia Britannica, 11th ed., vol. 24, p. 87. Cambridge, 1911. University Press.
- 10. WALLACE, C. L. H. Salt: in its relation to health and disease. Address delivered under the auspices of the London Vegetarian Society at Memorial Hall, London, March 24th, 1893.
- 11. ALLEN, F. M. Arterial hypertension. J. A. M. A., 74: 652, 1920.
- 12. ALLEN, F. M. and SHERRILL, J. W. The treatment of arterial hypertension. J. Metab. Research, 2: 429,
- 13. Ambard, L. and Beaujard, E. Causes de l'hypertension arterielle. Arch. gén. de méd., 1: 520, 1904.
- 14. BANG, H. O., BECHGAARD, P. and NIELSON, A. L. Low-salt diet in treatment of hypertension and hypertensive heart disease. Brit. M. J., 2: 1203,
- 15. Dahl, L. K. and Love, R. A. Relation of sodium intake to essential hypertension in humans. Fed. Proc., 13: 426, 1954.
- 16. Kempner, W. P. Treatment of kidney disease and of hypertensive vascular disease with rice diet. North Carolina M. J., 5: 125, 1944.
- 17. PRIDDLE, W. W. Observation on the management of hypertension. Canad. M. A. J., 25: 5, 1931.
- 18. THOMPSON, H. W. and McQUARRIE, I. Effects of various salts on carbohydrate metabolism and blood pressure in diabetic children. Proc. Soc. Exper. Biol. & Med., 31: 907, 1933-1934.
- 19. SELYE, H. and STONE, H. Role of sodium chloride in production of nephrosclerosis by steroids. Proc. Soc. Exper. Biol. & Med., 52: 190, 1943.
- 20. Sapirstein, L. A., Brandt, W. L. and Drury, D. R. Production of hypertension in the rat by substituting hypertonic sodium chloride for drinking water. Proc. Soc. Exper. Biol. & Med., 73: 82, 1950.
- 21. Fukuda, T. R. L'hypertension par le sel chez les lapins et ses rélations avec la glande surrénale. Union méd. du Canada, 80: 1279, 1951.
- 22. THOMPSON, W. F. Why don't the scientists admit they're human? Saturday Rev., 40: 44, 1957.
- 23. MENEELY, G. R., TUCKER, R. G., AUERBACH, S. H. and DARBY, W. J. Renal damage in rats fed large quantities of sodium chloride. Proc. Am. Soc. Clin. Invest., J. Clin. Invest., 31: 650, 1952.
- 24. MENEELY, G. R., TUCKER, R. G. and DARBY, W. J. Chronic sodium chloride toxicity in the albino rat. 1. Growth on a purified diet containing various levels of sodium chloride. J. Nutrition, 48: 489,
- 25. AUERBACH, S. H., TUCKER, R. G., DARBY, W. J. and MENEELY, G. R. Renal and vascular lesions induced in rats by a high salt diet. Fed. Proc., 12: 384,
- 26. MENEELY, G. R., TUCKER, R. G., DARBY, W. J. and NOVEMBER, 1958

- AUERBACH, S. H. Chronic sodium chloride toxicity in the albino rat. II. Occurrence of hypertension and a syndrome of edema and renal failure. J. Exper. Med., 98: 71, 1953.
- 27. MENEELY, G. R., TUCKER, R. G., DARBY, W. J. and AUERBACH, S. H. Chronic sodium chloride toxicity; hypertension, renal and vascular lesions. Ann. Int. Med., 39: 991, 1953.
- 28. BALL, C. O. T., TUCKER, R. G., DARBY, W. J. and MENEELY, G. R. Chronic sodium chloride toxicity: variation and correlation within groups of rats eating added salt. Proc. Am. Physiol. Soc., Am. J. Physiol., 179: 616, 1954.
- 29. LEMLEY-STONE, J., DARBY, W. J. and MENEELY, G. R. Body sodium and potassium in rats receiving increased dietary sodium chloride. Fed. Proc., 16: 78, 1956.
- 30. Meneely, G. R., Darby, W. J., Lemley-Stone, J., TUCKER, R. G. and BALL, C. O. T. Survival of rats prolonged by adding potassium chloride to diets containing toxic levels of sodium chloride. Proc. Am. Physiol. Soc., Am. J. Physiol., 187: 617, 1956.
- 31. YOUMANS, J. B. The chronic toxicity of salt (sodium chloride). J. M. A. State Alabama, 27: 161, 1957.
- 32. BALL, C. O. T. and MENEELY, G. R. Observations on dietary sodium chloride. J. Am. Dietet. A., 33: 366, 1957
- 33. Tucker, R. G., Ball, C. O. T., Darby, W. J., EARLY, W. R., KORY, R. C., YOUMANS, J. B. and MENEELY, G. R. Chronic sodium chloride toxicity in the albino rat. III. Maturity characteristics, survivorship and organ weights. J. Gerontol., 12: 182, 1957.
- 34. MENEELY, G. R., BALL, C. O. T. and YOUMANS, J. B. Chronic sodium chloride toxicity: the protective effect of added potassium chloride. Ann. Int. Med., 47: 263, 1957
- 35. Hubbell, R. B., Mendel, L. B. and Wakeman, A. J. A new salt mixture for use in experimental diets. J. Nutrition, 14: 273, 1937.
- 36. KERSTEN, H., BROSENE, W. G., JR., ABLONDI, F. and Subbarow, Y. A new method for the indirect measurement of blood pressure in the rat. J. Lab. & Clin. Med., 32: 1090, 1947.
- 37. Lapicque, L. Documents ethnographiques sur l' alimentation minérale. L'Anthropologie, 7: 35, 1896.
- 38. LEHMANN, C. G. Lehrbuch der Physiologischen Chemie, 2nd ed. Leipzig, 1853. Engelmann.
- 39. OSBORNE, T. B. and MENDEL, L. B. Inorganic elements of nutrition. J. Biol. Chem., 34: 131, 1918.
- von Bunge, G. Physiologische Chemie, 3rd ed. Leipzig, 1894. Verlag von F. C. W. Vogel.
- 41. Armstrong, S. (Editorial). The specificity hypotheses of psychosomatic medicine. Koch's postulates revisited. Am. J. Med., 24: 323, 1958.
- 42. Dahl, L. K., SILVER, L. and CHRISTIE, R. W. The role of salt in the fall of blood pressure accompanying obesity. New England J. Med., 258: 1186, 1958.
- 43. Dahl, L. K. Salt intake, adrenocortical function and hypertension. Nature, London, 181: 989, 1958.
- 44. KRAMER, S. N. and LEVEY, M. The Oldest Medical Text in Man's Recorded History: a Sumerian Physician's Prescription Book of 4000 Years Ago. In: Illustrated London News, vol. 226, p. 370. Strand, 1955. Ingram House.

Vitamin B12 Requirement of Adult Man*

William J. Darby, M.D., E. B. Bridgforth, A.B., Jean Le Brocquy, L.R.C.P., S.I., Sam L. Clark, Jr., M.D.,† Jose Dutra de Oliveira, M.D.,‡ John Kevany, M.B., Bch., William J. McGanity, M.D. and Carlos Perez, M.D.§

Nashville, Tennessee

The inconclusive state of knowledge concerning the human dietary requirement for vitamin B₁₂ is exemplified by the absence of a recommendation concerning this factor from the 1958 revision of the Food and Nutrition Board's Recommended Dietary Allowances [1]. The present report summarizes some observations which we have made on vitamin B₁₂-depleted persons, places these observations in relationship with other data, and derives therefrom an estimate of the dietary need of this vitamin in adult man.

We have elsewhere [2] compared the development of vitamin B_{12} deficiency in subjects with pernicious anemia, in gastrectomized patients, and in vegans, and have presented evidence for considering depletion in these three groups as a comparable event. Accordingly, we believe that appropriate observations on patients with pernicious anemia can be interpreted as indicative of the vitamin B_{12} requirements of normal man.

Patients with pernicious anemia in relapse were studied as vitamin B₁₂-depleted subjects. Many of the patients were previously well treated cases of pernicious anemia in whom relapse was purposefully induced by withholding specific therapy, and whose course of depletion was continuously observed [2]. None of the patients included in this series suffered from other chronic disease or experienced any episode of serious acute disease during the period of study. None of the histories or observations suggested dietary or other stress factors which might have aggravated the deficiency.

In all instances the initial dosages of the vitamin were deliberately very small in order to produce recognized but limited responses and to

minimize the storage and excretion of vitamin B₁₂. Hematologic criteria were adopted as the most satisfactory quantitative measures of adequacy of dosage. In each case a particular daily mean quantity of vitamin B₁₂ was administered for a sufficient period of time to permit stabilization of the hematologic response and assessment of the inadequacy of the dosage before an increased dosage level was instituted. The minimal dosage of vitamin B₁₂ required by a patient for the attainment and maintenance of a given hematologic status was thus titrated. We have considered this quantity to be equivalent to the amount of the vitamin utilized daily in metabolism plus excretory losses, but insufficient for building of body stores. From these findings, knowledge of the absorption of the factor from the gastrointestinal tract, and information about the dietary intake of vitamin B₁₂, we have deduced certain tentative conclusions regarding the daily requirement for vitamin B₁₂ by adult man. The present study was begun in 1948 and observations on several of the subjects predate that time. The major portion of the data was obtained prior to the existence of suitable methods for measuring vitamin B₁₂ levels in body fluids; hence, no data are presented on the variations in these levels.

SUBJECTS AND METHODS OF STUDY

The patients, all with proved pernicious anemia, were drawn from Vanderbilt University Hospital. Of the twenty subjects, twelve were men and eight were women. Four were Negroes, the remainder were white. The onset of pernicious anemia had ranged from one to twenty-one years prior to initiation of this study. The age at onset of the disease ranged from thirty-one to sixty-nine years, with a mean age of

^{*} From the Division of Nutrition of the Departments of Medicine and Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee. Supported in part by grants from the National Vitamin Foundation, Inc., the Nutrition Foundation, Inc., the National Institutes of Health, and the S. E. Massengill Company.

[†] Present address: Department of Anatomy, Washington University, St. Louis, Missouri.

[‡] Present address: Department of Clinical Medicine, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil. § Present address: Institute of Nutrition for Central America and Panama, Guatemala City, Guatemala.

TABLE I GENERAL DATA ON PATIENTS

AGE AT ONSE'T OF PERNICIOUS ANEMIA, DURATION OF DISEASE, SEX, RACE AND SYMPTOMATOLOGY

Patient No.	Age* at Onset (yr.)	Duration of Disease (yr.)	Sex	Race	Treatment before Relapse	Glossitis	Gastro- intestinal Symptoms	Neurologio Manifesta- tions
1	49	1	F	W		+	+	
2	53	10	M	W	L.E.†	+	+	+
2 3	58	1	M	W			+	
4	52	12	M	W	L.E.		+	
5	57	1	M	N			+	
6	55	11	F	W	L.E.	+		+
7	46	21	F	W	L.E.	+		+
8	66	8	M	W	L.E.			+
9	65	2	M	W	L.E.	+		+
10 .	60	1	F	W			+	+
11	53	1	F	W			+	+
12	31	20	M	N	L.E.			
13	44	1	F	W				+
14	44	5	M	W	L.E.	+	+	+
15	54	4	M	W	L.E.	+		+
16	33	12	F	W	L.E.	+	+	+
17	62	11	M	W	L.E.			+
18	65	4	M	W	L.E.	+		
19	53	1	F	N				+
20	39	- 6	M	N	L.E.	+		+

* Mean 51.9. Standard deviation 10.0.

† Liver extract.

fifty-two years. Seven of the patients were previously untreated, thirteen of them had been treated earlier with liver extract and, following interruption of maintenance therapy, had experienced a relapse. The course of relapse in these patients has been reported elsewhere [2].

The diagnosis of pernicious anemia was based in all cases on the clinical history, the presence of a macrocytic anemia, megaloblastic hyperplasia of bone marrow, histamine-fast achlorhydria, and a negative radiological examination of the gastrointestinal tract. In the thirteen patients previously observed under specific therapy, a good response to liver extract had been elicited.

The degree of anemia at the onset of the present study varied. For the previously treated patients several factors, social and medical, influenced the reinstitution of therapy. Treatment was initiated in the presence of less severe anemia in the patients who relapsed under observation than in those who relapsed due to self-interdiction of therapy or who were admitted to the hospital as new cases. The characteristics and symptomatology of the cases are presented in Table 1. Only the signs or symptoms noted at the onset of treatment are here recorded. There was a universal symptom of weakness of varying degree, one

patient (No. 5) presented with angina of effort, another (No. 1) with intermittent loss of vision. Ten patients exhibited glossitis, nine had gastrointestinal discomfort, and fourteen suffered paresthesias and reflex changes as evidence of neurologic involvement.

During the initial period of study each patient received daily treatment. A saline solution of the indicated quantity of crystalline vitamin B_{12}^* was given parenterally in the deltoid or gluteal region. Fifteen patients were initially hospitalized, the others were managed as outpatients. Organ meats were omitted from all the diets, which otherwise were unrestricted. During the maintenance study the patients received injections of vitamin B_{12} biweekly to monthly as outpatients.

For assessment of the initial response, the first fourteen days of therapy were chosen. Maximal hematologic responses are not obtained during this interval but it is sufficient time to assess degrees of hematologic response in relation to the dose administered. This period allows observation of maximal reticulocyte response, and is of such length that daily

* Vitamin B_{12} for these studies was generously supplied as Cobione® by Merck and Company, Inc. and in the later portion as Redisol,® injectable, by Merck Sharp and Dohme.

Table II
ERYTHROCYTE RESPONSES AT FOURTEEN DAYS AND RETICULOCYTE RESPONSES AS PERCENTAGES
OF STANDARDS

Patient No. Dosage of Vitamin B_{12} ($\mu g./day$)		Erythrocytes	Reticulocytes				
	Initial (million/cu. mm.)	14-Day Increase (million/cu. mm.)	Response (% of standard)†	Maximum (%)	Day of Maximum	Response (% of standard)	
1	0.25	1.07	0.41	62.5	67.7	7	178
2	0.25	1.36	0.95	79.0	25.2	7	81
2 3	0.25	1.37	0.52	51.0	19.0	7	62
4A*	0.25	1.55	0.66	57.5	8.5	9	31
5	0.25	2.00	0.82	82.0	11.5	7	60
6A	0.25	2.25	0.45	49.5	9.5	12	62
7	0.25	2.61	0.45	57.0	5.5	10	52
8A	0.30	2.78	0.49	66.0	5.0	4	57
9	0.5	1.19	0.80	63.5	21.8	10	62
10	0.5	1.32	0.23	19.0	32.5	11	102
11	0.5	1.35	1.30	107.5	27.0	5 .	86
12A	0.5	1.80	0.42	44.5	22.5	14	101
13	0.5	3.02	0.88	135.5	1.6	7	26
14	0.75	0.70	0.81	56.5	37.4	8	76
15	0.75	0.89	1.44	106.0	24.7	8	57
16	1.00	0.80	2.00	143.0	31.8	11	69
17	1.00	1.55	0.70	61.5	13.4	3	50
18	1.00	2.23	0.94	102.0	16.5	7	106
19	10.0	1.06	1.52	117.0	48.5	5	126

* Ambulatory

† Isaacs, R., Bethell, F. H., Riddle, M. C. and Friedman, A. J. A. M. A., 111: 2291, 1938 [4].

‡ Isaacs, R. and Friedman, A. Am. J. M. Sc., 196: 718, 1938 [5].

observation of patients may conveniently be made. The study of maintenance ranged over periods from fifty-five to 108 months.

Much evidence has accumulated that $1.0~\mu g$. daily of vitamin B_{12} , administered parenterally, is efficacious in the treatment of pernicious anemia. West and Reisner [3] early noted that approximately $1.0~\mu g$. daily was effective and that in one patient $0.1~\mu g$. per day proved ineffective. Accordingly, we adopted initial dosage levels ranging from $0.25~\mu g$. to $1.0~\mu g$. daily; one patient, for comparison, received $10~\mu g$. daily. The average dosages were then increased in the maintenance study to approximately $1.0~\text{to}~2.0~\mu g$. daily ($30~\mu g$. to $60~\mu g$. per four weeks), and eventually were raised considerably above these levels to test the effect of "maximal" doses.

In the initial period of response daily estimations were made of erythrocyte counts, hemoglobin concentration, reticulocytes and packed cell volume (PCV). These estimations (except for reticulocytes) were later repeated on the patient's return visits to the outpatient clinic throughout the follow-up. For purposes of brevity we are presenting tabular data during maintenance study on only the packed cell volume

and mean corpuscular volume (MCV). This latter criterion was selected because macrocytosis is a particularly sensitive early index of vitamin B_{12} deficiency as patients relapse [2], and appears even before definite identifiable anemia develops. The present studies show that in the reverse circumstance macrocytosis is also the last evidence of deficiency to disappear as vitamin B_{12} repletion occurs.

RESULTS

Initial Response Period of Fourteen Days. In order to appraise the adequacy of the initial responses at the several dosages, we have tabulated the data on erythrocyte increases in the fourteen-day period and the maximum reticulocyte responses for comparison with the standards of Isaacs et al. [4,5]. These standards were evolved from observations on patients with pernicious anemia who were judged to respond satisfactorily when treated with parenteral liver extract in adequate amounts. Table II summarizes the findings.

TABLE III

MAINTENANCE DATA

MEAN LEVELS OF PACKED CELL VOLUME AND MEAN CORPUSCULAR VOLUME

Patient No.	Mean	PCV	(%)		МС	eV (cu. micro	ons)		D
	B ₁₂ Dosage (µg./day)	Mean	S.D.	Mean	S.D.	No. of Readings	24622	p.,	Duration (mo.)
11	0.5	42.3 42.2	2.0	92.9 94.1	7.2 8.4	30 22	0.19	.843	39 22
13	0.5 1.0 2.0	44.5 44.2 45.1	0.5 2.1 2.8	115.1 94.8 94.0	10.9 12.2 7.3	14 42 32	6.19 0.65	<.001	4 40
20	0.2 0.4 0.5 1.0 2.0	40.7 44.4 45.8 48.0 47.4	1.5 1.8 2.1 1.7	126.7 104.1 108.6 96.8 95.5	8.1 12.9 11.4 6.2 7.3	14 13 12 41 30	5.47 0.85 4.75 1.14	<.001 .404 <.001 .255	33 12 12 8 41
18	0.2	42.6 46.6	4.0	95.6 89.0	5.9	21 37	5.17	< .001	33 5
15	0.7	43.9	2.2	99.8 93.2	8.6	18 35	2.58	.013	50 12
10	0.5 1.0 2.0	42.3 44.5 46.6	4.3 2.9 2.2	102.6 115.2 91.6	7.4 8.2 8.2	11 7 57	3.36 7.19	.004	96 3 3 71
6	0.5 1.0 2.0 4.0	39.8 40.5 38.7 36.5	2.3 0.7 1.5 2.8	123.9 112.0 99.5 100.4	14.9 7.6 9.3 10.3	22 12 32 27	0.97 2.12 0.34	.328 .040 .731	7 6 37 27

The limitation of the quantitative significance of the reticulocyte response relative to dosage is widely recognized. It is of some interest that our data do not reveal any obvious trend with dosage of B₁₂ in either time of attainment of maximum reticulocytosis or in the per cent of standard expected maximum. This is despite clear-cut differences in erythropoiesis.

It is evident from inspection of the data on erythrocyte response during the initial two weeks (Table II) that with dosages less than 0.5 μ g. per day of vitamin B₁₂ none of the patients exhibited the expected rate of erythropoiesis. At the dosage level of 0.5 μ g. per day two of the five patients attained the expected erythrocyte count by fourteen days, and above 0.5 μ g. four of the six patients attained such a level. Obviously, the minimal daily quantity of vitamin B₁₂ required for maximum erythro-

poiesis in depleted subjects approximates 0.5 to $1.0 \mu g$.

Maintenance Data. In Table III are summarized data on the long-term follow-up of a group of seven patients selected from the series on the basis of continued absence of acute disease and regularity of attendance and treatment over several years. The duration of observation at a given dose of vitamin B_{12} varies considerably because the dosage was altered only after it was evident that the patient had stabilized at the existing level of treatment.

Mean values for each level of intake are given along with the respective standard deviation. In the case of the mean corpuscular volume, statistically significant difference between the means for successive dosage levels is specified by a value of "P" (t test). The packed cell volume serves as an indication of absence of severe

degree of anemia at all levels and minimal changes in these levels with variation in intake is to be expected in view of the coincident alterations in cell size. As previously stated, the adequacy of vitamin B_{12} supply can be reasonably assessed from observation of the mean corpuscular volume; any value greater than 100 cu. microns is here considered macrocytic. We have adopted this value, somewhat greater than the one usually employed, as the upper limit of normal in order to allow for the occasional case of pernicious anemia which we have noted does not respond to maximal therapy with any agent by attainment of a MCV in the low 90's.

It is evident in patient 11 that no further improvement of the hematologic picture followed increase of vitamin B_{12} intake from $0.5~\mu g$. to $1.0~\mu g$. per day. Therefore it may be assumed that this patient's utilization of B_{12} was in the region of $0.5~\mu g$. per day, probably slightly less. This conclusion is in agreement with results in the initial study when this patient demonstrated a maximal fourteen-day response at the level of $0.5~\mu g$.

Patient 13 failed to maintain completely normal hematologic values on a daily level of $0.5~\mu g$., but attained these when the dosage was set at $1.0~\mu g$. daily. These findings, together with the patient's initial excellent response to the dose of $0.5~\mu g$. daily, indicate a utilization rate of somewhat less than $1.0~\mu g$. daily, but slightly greater than $0.5~\mu g$. A further increment of vitamin B_{12} to $2.0~\mu g$. daily was without additional effect.

Patient 20 showed progressive hematologic improvement as the dosage was adjusted successively in amounts of 0.18, 0.36, 0.5 to 1.0 μ g. daily. No further change occurred when the quantity was doubled to 2.0 μ g. daily. The minimal utilization for maximal maintenance seems to be slightly less than 1.0 μ g. per day for this patient.

Patient 18 exhibited a highly significant decrease in MCV and an increase in PCV when the mean maintenance dosage of vitamin B_{12} was raised from 0.2 μg . to 1.0 μg . per day. Earlier observations on his initial response had shown that a maximal fourteen-day response occurred with a dosage of 1.0 μg . per day. Again, this patient's minimal needs appear to be less than this amount.

Patient 15 experienced initial erythropoiesis equivalent to the expected standard (Table II) on a regimen of $0.75 \mu g$. of vitamin B_{12} daily. He

was maintained for a year on an average daily quantity of 0.7 μ g., but when the dosage was doubled to 1.4 μ g. a significant decrease in the MCV and an increase in PCV resulted. (Table III.)

Patient 10 exhibited a limited rate of initial erythropoiesis at a level of 0.5 μ g. daily (Table II), and in the maintenance period demonstrated a persistent macrocytosis until the dosage was increased above 1.0 μ g. daily. This patient's demands for vitamin B₁₂ are obviously greater than 0.5 μ g. daily.

Patient 6 showed a definitely substandard initial response to $0.25~\mu g$. of vitamin B_{12} . She maintained a nearly acceptable PCV on a regimen of $0.5~\mu g$. per day, but did not exhibit minimum MCV until the dosage exceeded $1.0~\mu g$. per day. Despite prolonged treatment with $2.0~\text{or}~4.0~\mu g$. per day the MCV in this patient never quite attained the expected normal. It appears that she has a requirement greater than $1.0~\mu g$. per day and that she also represents an example of a subject with pernicious anemia in whom the MCV does not return to within the usual accepted limits of the lower 90's even with relatively massive therapy.

Additional maintenance data in patients in whom the dosage of vitamin B_{12} was increased to 4.0 μg . daily showed that in only one of three was there any hematologic effect to be noted as a result of quantities greater than either 1.0 or 2.0 μg . In this one instance an increase of vitamin B_{12} dosage from 2.0 to 4.0 μg . was followed by a significant reduction of macrocytosis with an inconsequential alteration in the PCV.

COMMENTS

These data on maintenance utilization of vitamin B_{12} show that the minimal daily dose of the parenterally administered vitamin necessary for long-term support of maximal erythropoiesis in previously depleted patients with pernicious anemia varies from approximately 0.5 μ g. to slightly over 1.0 μ g. daily. No greater effect was detected in one instance by increasing the dose above 0.5 μ g., in two by increasing it from 1.0 to 2.0 μ g., or in two by increasing it from 2.0 to 4.0 μ g. In only one instance was an increase above 2.0 μ g. daily followed by a detectable change. It seems justifiable to conclude, therefore, that maintenance of maximal erythropoiesis requires the daily utilization of

from 0.5 to 2.0 μ g. of vitamin B₁₂. In most subjects the quantity appears to be between 0.5 and 1.0 μ g. These data on maintenance are consistent with the observations on initial responses which appear likewise to focus the quantity necessary for maximal initial response within the range of 0.5 to 1.0 μ g. It might have been expected that an estimate based on the quantity required to initiate response would tend to overstate the minimal requirement as determined for maintenance. It is surprising, therefore, to observe the quantitative agreement which obtained.

The dosage schedule adopted was such as to minimize excretory loss and to approach as economical a utilization of the vitamin as might occur under usual physiologic conditions. It is known, for example, that at dosages below 40 μ g. the excretion of vitamin B₁₂ is seldom greater (and usually less) than 10 per cent of the quantity administered parenterally [6]. At the smaller dosages the excretory loss is inappreciable [6,7]. Furthermore, some evidence exists for an unsaturation effect in the patient with pernicious anemia in relapse [8,9], an effect which would further favor economical use of the vitamin in our subjects who were not permitted to replenish body stores to a high level. Accordingly, we believe that our data may be taken as indicative of the quantity of vitamin B₁₂ normally required for the maintenance of hemopoiesis and other usual physiologic functions, including excretory losses.

The range of these quantities is between 0.5 and 2.0 μ g. per day. When supplied from the diet these amounts are derived from three meals per day, each of which might be expected to contribute equally. From studies [10] on the absorption of vitamin B₁₂ by healthy adults one may then place the total minimal quantity which would be required in the daily diet at 0.6 to 2.8 μ g. Indeed, for the narrower range of 0.5 to 1.0 μ g., which seems to suffice for most subjects, the dietary requirement would be between 0.6 to 1.2 μ g. daily.

It is of interest to examine these estimates of dietary needs in relation to the dietary content of the vitamin. Relatively few data are available on actual dietary intakes of vitamin B₁₂. In a recent study, however, Chung et al. [11] determined microbiologically the vitamin B₁₂ content of a series of diets. The mean vitamin B₁₂ content of one-day diets designed to meet the Recommended Dietary Allowances was 16.0 µg.

and 31.0 μ g., respectively for a low-cost and a high-cost menu group. A series of nutritionally poor diets designed after the most inadequate ones recorded in the Vanderbilt Cooperative Study of Maternal and Infant Nutrition [12] provided an average of 2.7 μ g. of B₁₂ daily. It is of interest that no macrocytic anemia of pregnancy was detected among women in this study. Clearly, it is easily possible with American food habits for the adult to obtain sufficient vitamin B₁₂ unless he rigidly restricts himself to food products entirely of plant origin.

It is worth pointing out also that in those cases studied at critically low dosage of vitamin B₁₂ during initial response and then with long-term maintenance at submaximal levels there was good correspondence between the dosage requirements at both periods. In other words, the patients who exhibited good initial response to the smallest dosages were those who required the least quantities for maintenance and vice versa.

It should be emphasized that despite submaximal treatment, often for years, none of these subjects exhibited any progression of existing neurologic signs or symptoms. This observation is consistent with the findings during relapse [2] and indicates that the requirements of the nervous system for vitamin B₁₂ have precedence over those of the hematopoietic system. In our clinical observations on these patients we have seen no other finding (glossitis, weight change, subjective symptoms, gastrointestinal symptoms or the like) which is so clearly an index of inadequate therapy as macrocytosis, nor any that requires as great a quantity of vitamin B₁₂ for reversal. Hence, we believe that careful estimates of erythrocyte size should be made in all instances when one is seeking to determine vitamin B₁₂ nutriture. Our observations further indicate that therapeutic trials for the detection of minimal vitamin B12 deficiency can be based upon meaningful reductions in mean corpuscular volume even in the absence of other clinical alterations.

SUMMARY

1. Patients with pernicious anemia in relapse have been studied as examples of vitamin B_{12} -depleted subjects. A critical study of the minimal dosage of parenterally administered vitamin B_{12} required for initial response and the long-term maintenance of these patients has been made. From these data estimates of the dietary requirement of vitamin B_{12} have been derived.

2. The data on initial response and on maintenance consistently indicate a daily utilization of vitamin B_{12} ranging from 0.5 to 2.0 μ g., the more usual range being 0.5 to 1.0 μ g. Considering the efficiency of absorption by normal persons of quantities of this order of vitamin B_{12} we estimate that the minimal daily dietary needs for this vitamin may be met by approximately 0.6 to 2.8 μ g., with a narrower range of 0.6 to 1.2 μ g. sufficient for most persons.

3. Long-term observations on patients receiving smaller than minimal dosage indicate that the demands of vitamin B_{12} for hemopoiesis exceed those for other clinically recognized physiologic functions, and that macrocytosis is the most sensitive indicator of vitamin B_{12} deficiency. In appraising vitamin B_{12} nutriture careful estimates of erythrocyte size therefore are important.

REFERENCES

Committee on Dietary Allowances, Food and Nutrition Board. Recommended dietary allowances (revised 1958). Publication 589, National Academy of Sciences—National Research Council, Washington, D. C.

 DARBY, W. J., JONES, E., CLARK, S. L., McGANITY, W. J., DUTRA DE OLIVEIRA, J., PEREZ, C., KEV-ANY, J. and LE BROCQUY, J. The development of vitamin B₁₂ deficiency by untreated patients with pernicious anemia. Am. J. Clin. Nutrition, 6: 513,

1958

West, R. and Reisner, E. H. Treatment of pernicious anemia with crystalline vitamin B₁₂. Am. J. Med., 6: 643, 1949.

 ISAACS, R., BETHELL, F. H., RIDDLE, M. C. and FRIEDMAN, A. Standards for red blood cell increase after liver and stomach therapy in pernicious anemia. J. A. M. A., 111: 2291, 1938.

 Isaacs, R. and Friedman, A. Standards for maximum reticulocyte percentage after intramuscular liver therapy in pernicious anemia. Am. J. M. Sc.,

196: 718, 1938.

 MOLLIN, D. L. and Ross, G. I. M. Vitamin B₁₂ concentrations of serum and urine in the first 72 hours after intramuscular injections of the vitamin. J. Clin. Path., 6: 54, 1953.

 CONLEY, C. L., KREVANS, J. R., CHOW, B. F., BARROWS, C. and LANG, C. A. Observations on the absorption, utilization, and excretion of vitamin B₁₂. J. Lab. & Clin. Med., 38: 84, 1951.

 UNGLAUB, W. G., MILLER, O. N. and GOLDSMITH, G. A. Saturation studies with vitamin B₁₂ in human subjects. Fed. Proc., 15: 374, 1956.

 SOKOLOFF, M. F., SANNEMAN, E. H. and BEARD, M. F. Urinary excretion of vitamin B₁₂. Blood, 7: 243, 1952.

- GLASS, G. B. J. Biochemistry and physiology of Castle's intrinsic factor and its relationship to the metabolism of vitamin B₁₂. Rev. d'hémat., 10: 137, 1955.
- Chung, A., Pearson, W. N., Darby, W. J., Goldsmith, G. A. and Miller, O. N. Estimates of the folic acid, vitamin B₆, pantothenic acid and vitamin B₁₂ intake of adult humans by dietary analysis. To be published.
- 12. Darby, W. J., McGanity, W. J., Martin, M. P., Bridgforth, E., Densen, P. M., Kaser, M. M., Ogle, P. J., Newbill, J. A., Stockell, A., Ferguson, M. E., Touster, O., McClellan, G. S., Williams, C. and Cannon, R. O. The Vanderbilt cooperative study of maternal and infant nutrition. iv. Dietary, laboratory, and physical findings in 2,129 delivered pregnancies. J. Nutrition, 51: 565, 1953.

End of Symposium on Nutrition in Internal Medicine

Kinetocardiographic Changes as the Result of Mitral Commissurotomy*

E. E. EDDLEMAN, JR., M.D. Birmingham, Alabama

THE present communication presents the preand postoperative kinetocardiographic findings in a group of patients with mitral stenosis in whom commissurotomy was performed.

PATIENTS

The twenty patients in this study were selected from a group in whom valvulotomy was performed for mitral stenosis at the University Hospital, and Veterans Administration Hospital, Birmingham, Alabama. These patients were chosen because kinetocardiographic records were obtained before and after the operation. The majority of patients in the group have been followed up for approximately two years after mitral surgery. In addition, several patients were included because of their unusual clinical and kinetocardiographic findings, although the follow-up period has not been as long.

Table 1 represents the classification of the various patients into special groups to facilitate subsequent discussion. As this is a small and select series, analysis of the clinical features will not be undertaken, and only the data relevant to the interpretation of the kinetocardiograms are presented in Table 1. The functional class of patients, as listed, is based upon that of the American Heart Association, and the presence of right-sided congestive heart failure is noted in each instance (indicated by the presence of pedal edema, enlarged liver, and an elevation in venous pressure). It is obvious from Table 1 that many of the patients in all groups were of the same functional class before surgery for mitral stenosis, while the results following the procedure varied considerably.

TECHNICS

Low frequency precordial movements (kinetocardiograms) were recorded using the technic previously described [1]. This includes a displacement pickup device (bellows and piezoelectric transducer) which is mounted on a crossbar above the thorax so that absolute chest wall movements are obtained. These do not represent relative interspace motion, as would be primarily recorded by any pickup device that rests directly upon the chest wall. The carotid pulse and lead ii electrocardiogram were recorded simultaneously with the kinetocardiogram, using a Sanborn Polyviso instrument in order to determine the time relationships of the various events. Kinetocardiographic records were obtained from various points over the precordium, corresponding to the "v" leads of the electrocardiogram and labeled K1, K2, etc. An additional record was usually obtained from the point of maximum apical impulse, if it occurred outside the usual recording points. The analysis of the normal patterns [2,3], and the configurational changes in "pure" mitral stenosis [4], mitral insufficiency [5], and aortic insufficiency [6] have been reported elsewhere. Patients were studied preoperatively and at frequent postoperative intervals, usually ten days, six weeks, six months, one year and two years, and in one instance as long as four years after mitral surgery.

RESULTS

Figure 1 illustrates the typical configurational changes of pure mitral stenosis, pure mitral insufficiency, and pure aortic insufficiency, as

^{*} From the Department of Medicine, Medical College of Alabama, and the Medical Service of the Veterans Administration Hospital, Birmingham, Alabama. Aided by a grant H-1912 from the United States Public Health Service, National Heart Institute.

TABLE I DATA RELEVANT TO INTERPRETATIONS OF KINETOCARDIOGRAMS

Patient No., Age (yr.)	Respiration Symptoms	Hemop- tysis	RCHF	O.S.	Pre- opera- tive Systolic Mur- mur*	ECG- QRS Axis	Valve Size†	Separation	Pre- operative Functional Class	Postoperative Function Class (1 yr.)	Post- operativ Functio Class (2 yr.)
	± ± ± ± ± ± ± ± ± ± ± ± ± ± ± ± ± ± ±			-	Marked I	mprovement	Which Continued				
1, 24 2, 39 3, 39 4, 17 5, 33 6, 31	Moderate Moderate-severe Moderate-severe Severe Severe Severe	Yes No Yes No Yes Yes	Yes No No Yes Slight Slight	Yes Yes Yes No No	No No Grade 1 No No Grade 2	90°NS 60°NS 90°NS 68°NS 85°AF 107°AF	2 mm. 3 mm. .34 cm. .4 cm. Very smali Pinpoint	1½ FB 2 FB 2 cm. Fair Wide NF, di- lated	IV III III-IV III-IV IV	I-II I I I	1 1 1 1
					Initial Imp	vovement — I	Vorse Second Year				
7, 39 8, 35 9, 32	Moderate Moderate Moderate	No Yes Yes	Slight No No	No Yes No Yes	Grade 3 No No	100°NS 98°NS 95°NS	Calcified valve, .5 cm5 cm3 cm.	2 FB 3-4 cm. Index fin- ger Wide	III-IV III III	tt t-tt	11-111
11, 27	Slight	Yes	No	No	Grade 2	70°NS	Very small	Wide	II	1	ttt
				Sl	ight Improve	ment-No I	mprovement — Wor	se			
12, 54 13, 37 14, 57	Severe Moderate-severe	No Yes No	Yes Yes No	Yes No No	Grade 1 Grade 3	45°AF 120°NS 114°NS	Pinpoint Small tear shape .4 cm.	3½ finger 1½ cm. 3 cm.	IV III-IV	III-IV III-IV	IV IV II-III
					Improved	but Recurre	nt Hemoptysis				
15, 33	Minimal	Yes	Yes	No	Grade 2	90°NS	Very small	Wide	11	1	1
					Mitral Ste	nosis and A	ertic Insufficiency				
16, 48 17, 31	Moderate Moderate	No Yes	Slight No	No No	No No	30°AF 80°NS	Small Tip of finger	2 cm. NF · 2½ FB	111	III	111
					Mitral In	sufficiency a	ter Operation				
18, 19	Moderate	Yes	No	No	No	89°NS	.6 cm.	Wide	8118	ı-н (1 yr. 6 mo.)	
					Mit	ral Insufficie	ncy Only				
19, 23	Moderate Moderate	No Yes	No Yes	No No	Grade 4 Grade 4	80°AF 80°NS	3 FB open Wide		111		III-IV

Note: Respiratory symptoms = the degree of exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, evaluated and graded.

RCHF = the presence of right-sided failure noted as indicated by pedal edema, enlarged liver, prolonged circulation time and elevated venous pressure.

and elevated venous pressure.

O.S. = opening snap.

N.S. = normal sinus.

A.F. = auricular fibrillation.

Functional Class = that of the American Heart Association.

FB = fingerbreadth.

* Systolic murmur graded according to the usual classification of Levine.

† Valve size pre- and postvalvulotomy is based only on the estimation of the surgeon at operation.

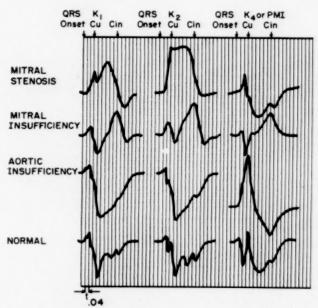


Fig. 1. The general configuration of the kinetocardiograms in patients with pure mitral stenosis, pure mitral insufficiency, and pure aortic insufficiency as contrasted with that in normal subjects. The onset of the QRS complex in the electrocardiogram is indicated by the first arrow. "CU" represents the upstroke in the carotid pulse and "CIN" the carotid incisural notch. Note that in pure mitral stenosis the outward movement in K₁ and K₂ is approximately .04 second after the onset of the ORS complex and is only temporarily interrupted by a brief inward motion during the early part of injection. The outward movement is quite pronounced and accounts for the palpable precordial "heave" that lasts throughout most of injection. The patients with mitral insufficiency have records which differ from those noted in mitral stenosis primarily by the presence of a late systolic outward movement usually present over the entire precordium and terminating approximately at the time of the carotid incisural notch. However, in some instances this late outward movement may be present only in a localized position such as K3 or K4. Records from patients with aortic insufficiency are characterized by a marked retraction of the precordium during injection in the parasternal region of the chest (K₁ and K₂), and a large outward movement followed by a marked retraction during ejection at the point of the apical thrust. The differences of these records from the normal pattern is obvious.

contrasted to the normal pattern. It is presented as a reference for the changes encountered in some of the various forms of valvular heart disease. Figure 2 contrasts the three types of kinetocardiographic preoperative patterns found in mitral stenosis [4], which were previously divided into these classes for descriptive purposes only; however, as will be noted in the following discussion, these forms may have a more fundamental significance. In all instances of pure mitral stenosis, the records are characterized by

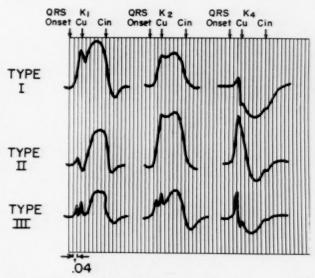


Fig. 2. The significant features of the three types of patterns noted in patients with pure mitral stenosis. 'CU" represents the upstroke in the carotid pulse and "CIN" the incisural notch. Group 1 is characterized by large early systolic outward movement occurring approximately .04 second after the QRS complex and is maximum over the lower right parasternal region of the chest (K1). It is usually associated with an inward movement or at most a very small outward movement at K4. In group 11 the outward movement over the precordium is most pronounced over the left precordium, usually being maximum at K4. However, in some instances it is equally large at K2, but always minimal at K1. Group III is characterized primarily by the fact that the outward movement over the precordium is double in configuration rather than singular. (These make up a very small percentage of the patients with mitral stenosis.) It is possible that the double outward movement may be related in some way to the loud first heart sound. No clinical significance could be attributed to this third

an early outward movement over the precordium, occurring approximately .04 second after the onset of the ORS in the electrocardiogram. This is followed by a small brief retraction, or inward movement of the chest wall synchronously with the onset of the upstroke in the carotid pulse. The precordium then moves outward again, reaching a peak in mid-systole and begins returning to the diastolic baseline usually before the end of ejection which occurs about .04 second before the carotid incisural notch. Thus the records reveal a rather sustained outward movement (precordial heave), located over the entire precordium during systole, which in most instances is easily palpable at the bedside. In the group I records this outward movement of the chest wall is most prominent over the lower right parasternal region of the chest (K₁) and there is usually inward movement at the

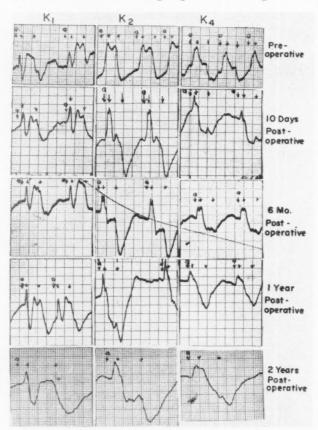


Fig. 3. Kinetocardiograms from a patient with pure mitral stenosis who had an excellent clinical result which continued during the two-year follow-up period (patient 5). The kinetocardiograms are those taken before operation, ten days, six months, one year and two years after mitral commissurotomy. Note the typical configuration of preoperative tracing and the alterations which recurred in the K1, K2, and K4 positions after valvulotomy. All but the last trace was taken at paper speed of 25 mm. per second while the last one was taken at a paper speed of 50 mm. per second. The onset of the QRS complex of the electrocardiogram is noted in each tracing by an arrow designated "Q". The following arrow indicates the onset of injection as determined by the upstroke in the simultaneous carotid pulse and the second arrow the carotid incisural notch. Note that there appears to be a gradual change from the preoperative trace until the trace one year after operation, while there is no appreciable further change at two years. The initial alteration which occurred is most prominent in the K2 trace and is manifested by a decrease in the outward movement in mid-systole. This gradually progresses and is further reduced until the trace at one year shows almost no midsystolic outward movement at all. It is interesting that some change occurred as early as ten days after the surgical procedure. The initial outward movement after the onset of the QRS complex was gradually reduced in relative amplitude until at two years it is almost normal in amplitude. Note that in addition to the decrease in these motions the retraction of the precordium during the ejection period gradually increases until it becomes the most predominant feature in the trace while in the control trace it was almost absent. Although the final traces at two years are not entirely normal the main features of a

apical region (K₄) at the same time. (Fig. 2.) These patients frequently have right axis deviation in the electrocardiogram. Group II has a relatively smaller initial outward movement in the right lower parasternal region of the chest. This outward movement is usually much larger in K₂, and is often of even greater amplitude in the K₄ or apical region of the chest. It is important to point out that this is a generalized precordial outward movement, and not limited to the apex. Occasionally, a tracing at the apex may resemble that of aortic insufficiency (Fig. 1); however, if records are obtained from the K₁, K₂ and K₃ positions as well, it is apparent that this outward movement is represented in the other areas and is not an isolated thrust in the apical region. This apparently accounts for the occasional patient with pure mitral stenosis who has a palpable apical thrust which resembles left ventricular hypertrophy at the bedside. Again, it is usually distinguishable from the impulse of left ventricular hypertrophy by the fact that it is part of a generalized precordial thrust. This has been discussed elsewhere [7]. In the second group, no instance was encountered (except one patient with a deformity of the chest wall which displaced the heart rightward) in whom right axis deviation (more than 90 degrees) was present in the electrocardiogram, although most of the axes tended to be vertical. Type 3 is characterized by a double rather than single outward movement in early systole (pre-ejection). One of these kinetocardiographic patterns has been uniformly present in a large group of patients with mitral stenosis, only a few of whom are considered in detail in this study. Up to the present time no exceptions have been encountered; however, it is important to point out that these patterns are not considered diagnostic of mitral stenosis per se in that patients with right ventricular hypertrophy due to other causes may reveal some of the same features; the differences have not as yet been clearly defined in this laboratory.

Patients Markedly Improved. The first group of patients in this series, as classified in Table I, represents those in whom striking improvement from mitral valvulotomy occurred. All six of

normal kinetocardiogram are present. However, the apical thrust is still poorly defined and is probably represented only by the second notch after the initial upstroke in the K_4 trace. The other patients in this group also had traces that resembled even more closely the normal pattern with a decrease in the early anterior systolic outward movement and a well defined retraction during ejection.

these patients have become essentially asymptomatic and have shown objective clinical improvement as indicated by a decrease in heart size, decrease in left auricular enlargement, reversion of the electrocardiogram toward normal, decrease in venous pressure and circulation time, and an increase in vital capacity. Two of these patients were in marked right-sided congestive heart failure before operation which had cleared entirely when last observed. Two of the patients (Nos. 2 and 3) were only moderately incapacitated compared to the other four. Their ages ranged from seventeen to thirty-nine years and no obvious clinical reason could be found to explain why these particular patients obtained such excellent results from the operation. All the patients had a small mitral valve opening at operation. It is interesting that the two who had preoperative cardiac catheterization revealed moderately elevated pulmonary artery and pulmonary capillary wedge pressures in the presence of normal blood flow (cardiac index).

All six patients in this group had preoperative kinetocardiograms which were classified in group II and all had a reversion of their abnormal kinetocardiographic findings toward normal. (Fig. 3.) Reversion apparently was slow as some changes occurred as late as one year after mitral valvulotomy. The initial changes appeared to be a relative decrease in the mid-systolic outward movement which is usually most prominent in the K_2 position, and an increase in retraction of the chest during ejection (greatest in amplitude at the apical region). These changes were noted as early as ten days after the operative procedure but improvement occurred as late as one year after operation.

In summary, these patients represented a somewhat heterogenous clinical group; however, all had similar kinetocardiograms, and all had reversion of the kinetocardiogram toward normal paralleling their clinical improvement. All of these patients remained essentially asymptomatic during the postoperative period.

Patients with Initial Improvement, but Worse the Second Year. In the second group, five patients had moderate to striking improvement during the first year, followed by clinical deterioration during the second year. Two patients (Nos. 8 and 11) during the second year returned to their preoperative states, or even to a more deteriorated clinical condition. The kinetocardiograms in this group never reverted to normal at

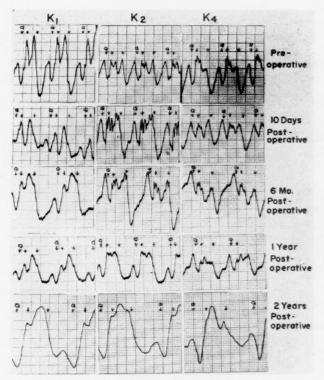


Fig. 4. Traces obtained from a patient in group ii in whom there was an initial clinical improvement for the first year postoperatively but later deterioration so that at the second year the patient was clinically worse than he was preoperatively (patient 8). Again the onset of the QRS is indicated by the arrow labeled "Q." The following arrow indicates the onset of ejection as determined by the upstroke of carotid pulse and the next arrow the carotid incisural notch. The last tracing at two years was taken at 50 mm. per second of paper speed rather than at 25, which accounts for the apparent differences in appearance. Note that there are only very minor differences in any of the traces, preoperatively, ten days or even up to two years postoperatively even though the patient, at the six months and one year period, had marked clinical improvement and was almost asymptomatic. The precordial heave or the early anterior systolic outward movement of the precordium is still present equally well throughout all traces and the minor differences in appearance can be explained by changes in recording sensitivity. Although this patient had marked clinical improvement initially, precordial traces did not change and subsequently the patient's clinical status deteriorated until at two years he was clinically worse than at time of operation even though, as far as one can judge, the operative procedure was satisfactory. This would suggest that either the pulmonary hypertension as a result of the mitral stenosis was fixed and therefore mitral surgery was ineffective or there were myocardial changes which were no longer reversible.

any time during the postoperative period, and in general were unchanged (Fig. 4); however, two patients did have records that appeared to be slightly improved at one year (a relative decrease in outward movements and a relative increase



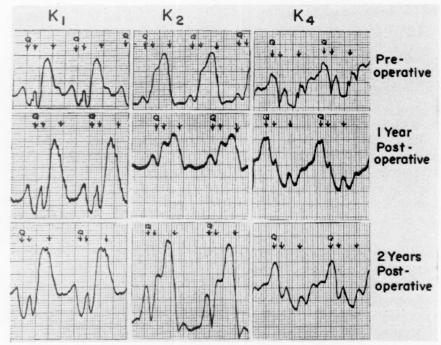


Fig. 5. The control, one year, and two-year postoperative traces in a patient who never demonstrated any clinical improvement (patient 13). Note that there are very few changes in the kinetocardiograms and what differences there are can be attributed primarily to a change in recording sensitivity.

in the retraction during ejection), but later reverted to essentially the same general pattern as that noted preoperatively. None of these patients had a type 2 kinetocardiographic pattern.

Patients Slightly Improved, Unimproved, or Worse Than Before Operation. The three patients in this category, as noted in Table 1, had type 1 preoperative kinetocardiographic configuration. In addition, no significant change in the kinetocardiograms occurred after mitral valvulotomy. (Fig. 5.) It is interesting to note that two of these three patients had chronic pulmonary disease associated with the mitral stenosis.

The remaining sub-groups are listed primarily because of the unusual kinetocardiographic findings and for their possible implications in the preoperative evaluation of patients with mitral valve disease.

Excellent Clinical Results, Except for Recurrent Hemoptysis. One patient, although he had only minimal difficulty before operation, became asymptomatic during the two-year postoperative period except that during the second year he had two episodes of hemoptysis without any other symptoms. Bronchoscopy following one of the episodes of hemoptysis revealed large tracheal and bronchial varices. The kineto-

cardiographic pattern from this patient returned essentially to normal. In addition, there has been no evidence following commissurotomy of any recurrence of shortness of breath, elevated venous pressure, decrease in vital capacity, or any other signs of clinical deterioration. This possibly illustrates an unusual instance in which endobronchial varices, that presumably were present before operation, may have remained and were still subject to bleeding episodes even after the mitral block was relieved by surgery.

Patients with Aortic Insufficiency in the Presence of Mitral Stenosis. There were two patients who had aortic insufficiency in the presence of classic physical signs of mitral stenosis. Cardiac catheterization in the first patient revealed only slight elevation of the pulmonary artery and capillary wedge pressures. Studies before and after exercise did not reveal any catheterization evidence of a mitral block. This patient has had no improvement following operation.

The kinetocardiographic findings from this patient did not change following operation, and it is important to point out, as illustrated in Figure 6, that the patient's preoperative kinetocardiogram had very few features compatible with a predominance of right ventricular function or pure mitral stenosis. The only possible

suggestion in the records was a sharp early systolic outward movement over the precordium. However, instead of being followed by a small inward motion with the onset of ejection and a large mid-systolic outward movement, this patient's record revealed a marked retraction of the precordium during ejection, such as is noted in patients with aortic insufficiency. Thus the patient illustrates an instance in which mitral stenosis was considered to be the predominant lesion clinically, while neither kinetocardiographic nor catheterization studies revealed any evidence of a predominant mitral lesion. The superiority, in this subject, of the latter procedure is supported by the lack of postoperative improvement.

The other patient had similar physical findings of both aortic insufficiency and mitral stenosis; however, hemoptysis was a significant clinical feature. At operation, a small mitral valve opening was found and satisfactory separation of the cusps was obtained. The only clinical improvement, subsequently noted, has been the relief of hemoptysis. The preoperative kinetocardiograms (Fig. 7) had some features both of aortic insufficiency and mitral stenosis. The tracing in the region of the apex had a double outward movement (which has not been noted in mitral stenosis), followed by a marked systolic retraction, resembling that noted in early aortic insufficiency. However, the right parasternal region of the chest revealed characteristic findings of increased right ventricular function (mitral stenosis). Following operation, the kinetocardiographic traces changed (Fig. 7), and were then identical in all respects with those previously reported for aortic insufficiency. Thus the preoperative tracings had features resembling mitral stenosis, as well as aortic insufficiency, but after commissurotomy reverted to a pure aortic insufficiency-type tracing with a large localized apical thrust terminating abruptly about the time of ejection.

Mitral Insufficiency after Operation. One patient was found to have a small mitral opening at operation with no detectable insufficiency; however, following fracture of the cusps, a marked mitral insufficiency was detected by the surgeon. Subsequent to the operation, the precordial movements, which were type 3 originally, reverted from that of mitral stenosis to that of mitral insufficiency. (Fig. 8.) This was characterized by a late systolic outward movement, terminating about the time of the incisural notch

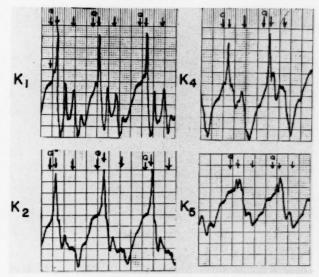


Fig. 6. The preoperative traces from a patient with mitral stenosis and aortic insufficiency in whom the mitral stenosis was considered to be the predominant lesion (patient 16). The arrow labeled "Q" indicates the onset of the QRS complex of the electrocardiogram, the next arrow the onset of the ejection as determined by the upstroke in the carotid pulse, and the second arrow the carotid incisural notch. Note that the traces bear very little resemblance to that usually noted in pure mitral stenosis. (Fig. 1.) The major difference is the marked retraction of the precordium during ejection. The early systolic outward movement is exaggerated over the precordium; however, this is not sustained as occurs in pure mitral stenosis. Note the double outward systolic movement in the K5 trace. The second component probably represents the apical thrust noted in aortic insufficiency as it has not been detected in patients with mitral stenosis in traces from this position. At operation this patient was noted to have predominant aortic insufficiency even though mitral stenosis was present. This patient has subsequently shown no improvement after valvulotomy.

in the carotid pulse. It is important to point out that this late outward systolic movement is frequently generalized over the entire precordium but may be detected only in specific areas of the precordium and in this instance was most prominent in the K_3 area.

Patients with Only Mitral Insufficiency. Two patients, in whom there was a grade 4 or louder systolic murmur, as well as a typical diastolic rumble, were found to have widely dilated mitral valves with no detectable evidence of stenosis at operation. Both these patients had precordial traces before surgery which were characteristic of mitral insufficiency, as previously reported [5], and characterized by a late systolic outward movement, reaching its peak approximately at the time of the carotid incisural notch. (Fig. 9.)

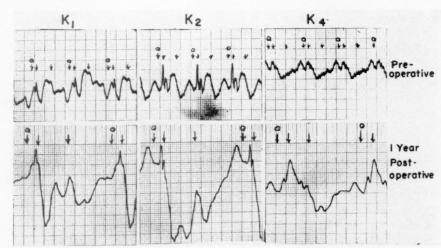


Fig. 7. The pre- and postoperative traces of a patient with both mitral stenosis and aortic insufficiency (patient 17). Note that the preoperative trace from the parasternal region of the chest resembles that usually found in mitral stenosis. However, the trace in the apex, although of poor quality, does show some of the features of aortic insufficiency. The trace taken one year after fracture of the mitral valve now resembles that noted for pure aortic insufficiency with a marked retraction of the parasternal region of the chest during the ejection period and a prominent apex thrust which terminates about the time of the onset of ejection $(K_4 \text{ trace})$. This is an example of a patient with both mitral stenosis and aortic insufficiency who was thought to have marked mitral stenosis, and the precordial traces were consistent with this opinion. However, after mitral commissurotomy the precordial trace changed to that of pure aortic insufficiency. This tends to support the concept that there is a correlation of the precordial movements with specific functionally significant valvular defects.

The records of seven patients who died either in the hospital or during the first year after operation were reviewed, but as no significant differences could be found in the traces they were not included in this series.

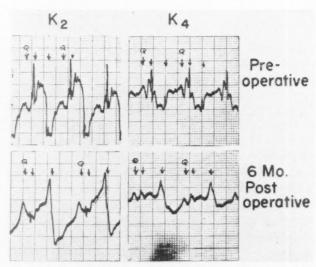


Fig. 8. The traces before and after operation in a patient in whom mitral insufficiency occurred after fracture of the posterior commissure (patient 18). Note that after six months there is a marked outward movement in late systole, reaching a peak just before the carotid incisural notch as indicated by the second arrow after the onset of the QRS complex. This pattern resembles that described in Figure 1 for pure mitral insufficiency.

COMMENTS

The full physiologic changes which result from mitral valvulotomy apparently are still under dispute. Although many patients improve subjectively, objective evidence of improvement has been much less impressive. Most observers have found that the pulmonary artery pressures may be minimally to moderately reduced or even unchanged after commissurotomy [8,9]. These changes may not necessarily parallel the subjective improvement. This and other evidence has led some to doubt the efficacy of the procedure in regard to its physiologic benefits, although the clinical improvement that most patients demonstrate has been uniformly accepted. Since it appears from our observations that the kinetocardiogram probably represents the most accurate means of evaluating right ventricular predominance or hypertrophy, and since these traces are related to movements of the heart, they therefore are directly related to the process of ventricular contraction and relaxation. Thus it appears likely that changes in these records may reflect postoperative alterations in heart function. The fact that a group of patients (six) did have reversion of the kinetocardiograms from that of typical right ventricular predominance to patterns which were almost normal in configuration offers evidence

that this hemodynamic process, at least in some patients with mitral stenosis, is entirely reversible. If the hemodynamics were not altered or alleviated, it is difficult to visualize how the precordial movements could change to an essentially normal pattern, as illustrated in Figure 3. However, some patients studied had only minor or no improvement in the traces, even after an apparently technically satisfactory mitral valvulotomy. This, in itself, would suggest that the pulmonary hypertension may have been irreversible, and therefore relieving the mitral block did not appreciably influence the contractile process of the right ventricle. An alternate explanation is that ventricular function may have deteriorated beyond the reversible stage due to myocarditis or other factors in the groups which had no kinetocardiograph reversion of their patterns. The fact that the initial patterns were somewhat different from those in whom the traces reverted to normal supports the latter concept. This emphasizes the importance of myocardial factors and function in determining the results from valvulotomy. In another group of patients deterioration in the clinical state occurred after an initial year of improvement. In most instances the kinetocardiograms demonstrated no change or improvement at any time. The fact that even after a technically successful valvulotomy, no significant changes occurred in the kinetocardiographic records at any time postoperatively even though the clinical condition improved temporarily appears to be important. This, in itself, emphasizes that the myocardial or pulmonary factors may already have been beyond the point of no return in these patients. The kinetocardiogram apparently indicated this abnormality before clinical evidence appeared. The possible aid by the kinetocardiogram in recognizing this preoperatively will be discussed subsequently.

Although this series is not intended to be an inclusive report of all patients subjected to operation, nevertheless it does illustrate instances in which the operation probably should not have been performed. The kinetocardiogram appears to offer some help along these lines. Both of the patients with pure mitral insufficiency at operation had well defined "mitral insufficiency" kinetocardiograms (Fig. 9), and one patient in whom mitral insufficiency was created at surgery subsequently exhibited changes in his kinetocardiogram from that of pure mitral stenosis to that of mitral insufficiency. (Fig. 8.) Thus these

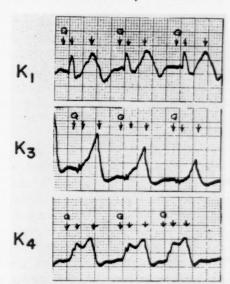


Fig. 9. Records obtained preoperatively in a patient who was clinically considered to have a predominant mitral stenosis but was found at operation to have only mitral insufficiency (patient 20). The "Q" indicates the onset of the QRS complex of the electrocardiogram, the following arrow the onset of ejection as determined by the upstroke in the carotid pulse, and the second arrow the incisural notch. Note the marked outward movement in late systole in all traces, terminating at or just before the carotid incisural notch. This tracing resembles those reported for pure mitral insufficiency, as illustrated in Figure 1. Thus the kinetocardiograms suggested a predominant mitral insufficiency which subsequently was proved although the clinical findings were considered to be indicative of mitral stenosis. This illustrates the possible use of the kinetocardiograms in determining which valve lesion is functionally significant.

observations appear to offer evidence that the kinetocardiogram can (in some patients at least) detect the presence of a predominant mitral insufficiency. Exactly how reliable the kinetocardiogram will be in evaluating the degree is not apparent from this study; however, it is our impression that a minimal or even moderate degree of mitral insufficiency is not or may not be detected in the precordial traces. Mitral insufficiency probably has to be functionally predominant over mitral stenosis in order to be clearly apparent in the kinetocardiogram; however, this in itself should prove useful.

One patient in this study had mitral stenosis and aortic insufficiency; however, cardiac catheterization did not show any significant mitral block. The kinetocardiographic traces also did not reveal any significant features of mitral stenosis but did have some features of aortic insufficiency. This further emphasizes the fact that the kinetocardiographic traces

apparently can be of aid in estimating which valvular lesion functionally predominates. In addition, the changing of a pattern (compatible with both mitral stenosis and aortic insufficiency) to that of pure aortic insufficiency by correcting the mitral valve lesion (Fig. 7), further emphasizes the value of the kinetocardiographic trace in registering hemodynamically significant valvular lesions.

The most important question that arises is whether the kinetocardiographic traces offer any evidence as to which patient will have the best clinical and hemodynamic results from the operation, as occurred in the first six patients in this series, and thus aid in a better selection of patients. This series is regrettably small; however, there are certain features in the traces which should be emphasized for future evaluation in order to determine if these patterns will be consistent. All the patients who obtained excellent results were preoperatively classified as group 11-type mitral stenosis, in which the early systolic anterior movement of the chest wall is of greatest magnitude in the region of the apex. None of the patients who later became clinically worse, or had no improvement of the clinical status, had this type of precordial trace. Further analysis of the first group of patients revealed several other interesting points. Two patients had preoperative cardiac catheterizations which revealed elevated pulmonary capillary wedge, as well as pulmonary artery pressures, but in the presence of a normal cardiac output. In addition, none of the six patients had electrocardiographic criteria of ventricular hypertrophy. Although these findings were uniform, the clinical status of the patients was not. Two of the patients were in severe right-sided congestive heart failure with an elevated venous pressure, enlarged liver and pedal edema, in addition to the usual symptoms of shortness of breath and hemoptysis; however, it should be pointed out that none of these patients had markedly enlarged hearts. From this it is apparent that the clinical status alone in these instances was not helpful in predicting the eventual outcome, whereas there were uniform and characteristic features in the kinetocardiogram. Thus it is possible that the kinetocardiogram may be useful in selecting patients before mitral valvulotomy who will obtain the most benefit. As stated, this series of patients is small and the observations obviously must be extended to a larger group before final conclusions can be reached in this regard.

Why those patients with predominant forward motion (type 2) exhibited more improvement than those with predominant rightward movement (type 1) is not clear; the possibility that this is a chance observation because of the relatively small number of patients cannot be excluded at present.

In addition to the possible potentialities of the kinetocardiogram in aiding the selecting of patients for mitral valvulotomy, it apparently can be useful in determining prognosis since those with no kinetocardiographic changes postoperatively had no lasting clinical improvement.

CONCLUSIONS

1. Kinetocardiographic tracings appear to be reliable in detecting major functional valvular heart lesions and in indicating which valvular lesion is hemodynamically predominant.

2. Kinetocardiographic evidence appears to indicate that in some instances the hemodynamic alterations resulting from mitral stenosis can be completely reversed by mitral valvulotomy.

3. All patients who improved strikingly following surgery and have continued to be asymptomatic have had the same general type of kinetocardiographic trace which is different from that noted in the patients in whom no improvement occurred or in whom the improvement did not last.

4. It is suggested that kinetocardiographic traces may aid in the differentiation and selection of patients for mitral operation.

5. Kinetocardiograms appear to aid in determining prognosis as those patients in whom no postoperative change occurred in the kinetocardiograms have deteriorated clinically even though they may have shown temporary improvement.

REFERENCES

- EDDLEMAN, E. E., JR., WILLIS, K., REEVES, T. J. and HARRISON, T. R. The kinetocardiogram. I. Method of recording precordial movements. *Circulation*, 8: 269, 1953.
- EDDLEMAN, E. E., JR., WILLIS, K., CHRISTIANSON, L., PIERCE, J. R. and WALKER, R. P. The kinetocardiogram. II. The normal configuration and amplitude. Circulation, 8: 370, 1953.

 EDDLEMAN, E. E., JR. and WILLIS, K. The kinetocardiogram. III. The distribution of forces over the anterior chest. Circulation, 8: 569, 1953.

EDDLEMAN, E. E., JR., YOE, R. H., TUCKER, W. T..
KNOWLES, J. L., WILLIS, K. The dynamics of
ventricular contraction and relaxation in patients
with mitral stenosis as studied by the kinetocardio-

- gram and ballistocardiogram. Circulation, 11: 774, 1955.
- 5. Tucker, W. T., Knowles, J. L. and Eddleman, E. E., JR. Mitral insufficiency: cardiac mechanics as studied with the kinetocardiogram and ballistocardiogram. Circulation, 12: 278, 1953.
- 6. EDDLEMAN, E. E., JR. Kinetocardiographic findings in
- aortic insufficiency. Am. Heart J., 53: 530, 1957.
 7. Eddleman, E. E., Jr., Hefner, L., Reeves, T. J. and HARRISON, T. R. Movements and forces of the
- human heart. 1. The genesis of the apical impulses. Arch. Int. Med., 99: 401, 1957.
- 8. GLOVER, R. P., O'NEILL, T. J. E., GREGORY, JOHN E. and FROIO, G. F. Results of the surgical treatment for mitral stenosis. Analysis of 100 consecutive cases. Circulation, 6: 321, 1952.
- 9. WOOD, J. A., ALEXANDER, J. K., FRANK, C. W., WEST, J. R. and RICHARDS, D. W. Some clinical and physiologic effects of mitral commissurotomy. Circulation, 13: 178, 1956.

A Quantitative Abnormality in Serum Mucoproteins in the Marfan Syndrome*

HABEEB BACCHUS, M.D.

Bethesda, Maryland

THE Marfan syndrome is characterized by a variety of morphologic abnormalities involving many organ systems, for example, arachnodactyly, vascular aneurysms, cystic lung disease and ocular disturbances. The authoritative review by McKusick [7] presents the clinical and genetic features of the syndrome in detail. In that analysis it was concluded that the syndrome is an "abiotrophy" involving connective tissues. Certain errors in connective tissue metabolism probably constitute the basic mechanism whereby tissues in various organ systems are involved.

The bulk of the literature on the Marfan syndrome has been concerned with the genetic. morphologic and pathologic aspects of the disease. An error in the formation of elastic tissue, as well as in the process of elastinolysis, have been suggested as contributory, if not basic, defects in this disease [2]. The precise nature of the abnormal connective tissue metabolism is not known however. In one study [3] a survey of various endocrine glands revealed no gross errors in these systems. It has been suggested that the morphology of the hard palate in the Marfan syndrome (gothic-arched palate) is related to abnormalities in the morphogenesis of the anterior pituitary. While the increase in bone length might be suggestive of excessive growth hormone, the other morphologic features, viz.. muscular development, are not suggestive of hypersomatotrophinism.

We have recently had opportunity to study a family in which the Marfan syndrome was found in six of eight siblings. The serum levels of mucoproteins, which are one of the constituents of connective tissue, were studied in these patients, and in normal control subjects. The data reveal that the serum level of mucoproteins in

patients with this syndrome is significantly less than in control subjects. The response of serum mucoproteins to an ascorbic acid load also was studied.

MATERIALS AND METHODS

The observations were made on members of a Negro family in which six of eight siblings have evidence of the Marfan syndrome. The patients were seen regularly in the Outpatient Department during the course of this study. The pertinent clinical data are presented in Table 1. The six patients in whom the diagnosis of the syndromes was made all had the features of arachnodactyly, winged scapulas, poor muscular development, gothic-arched palate and ocular disturbances. One of these also had a pigeonbreast configuration of the thorax. One patient had two episodes of pneumothorax, one associated with hemothorax; he was observed during one of these episodes. The mother of these children was also studied. She exhibited none of the diagnostic stigmas of the Marfan syndrome, and was included in the group of control subjects.

Control subjects were drawn from the Hospital House Staff, and from subjects of comparable ages and race attending the Outpatient Department. These control subjects were in good health. Serum mucoproteins were determined by the turbidimetric method of Popper et al. [4], based on the methods of Winzler [5]. All determinations were made in duplicate. Complete blood counts, urinalysis, and estimations of total proteins and globulin, calcium, phosphorus, protein-bound iodine and alkaline phosphatase, were made in these patients (but not in the control subjects); the usual clinical laboratory methods for these determinations were employed.

RESULTS AND OBSERVATIONS

Serum Mucoprotein Levels in Control Subjects and in Patients with the Marfan Syndrome. Duplicate analyses were made in all subjects. The data

* From the Department of Medicine, Providence Hospital, Washington, D. C.

TABLE I CLINICAL DATA IN THE FAMILY STUDIED

Subject, Age (yr.), Sex	Clinical Features and Diagnosis	Pertinent History	Clinical Laboratory Data		
Mother, 46, F	Essentially good health except for obesity; included in the control group	Grav. VIII, Para VIII; pneumonia in 1955	4% sickling; hemoglobin, 12.6 gm. %; hematocrit, 37% leukocytes, normal; urine negative		
Eldest son, 16, M	Fatiguability, dizziness; 78 inches tall; span 78 inches; hyperextensibility of elbow and finger joints, winged scapulas, gothic-arched palate, myopia and iridonesis, poor muscle development; decreased subcutaneous fat; Marfan syndrome	Good growth and development to age 6, when he started to grow tall and thin; non-paralytic poliomyelitis at age 7; pneumohemothorax, Feb. 1956; pneumothorax, March 1956	No sickling; hemoglobin, 13.1 gm. %; hematocrit, 41% leukocytes normal; other data within normal limits		
Eldest daughter, 14, F	Fatiguability, hyperextensi- bility of fingers, pigeon- breasted, gothic-arched pal- ate, myopia, thin muscles; Marfan syndrome	Tiredness and lethargy several months	No sickling; hemoglobin, 11.5 gm. %; hematocrit, 36% leukocytes normal; other data within normal limits		
Daughter, 12, F	Poor muscular development, hyperextensible elbow and finger joints, arachnodac- tyly, clavicular deformity, asymmetric trapezius, gothic-arched palate, de- pressed anterior lower chest, iridonesis and nystagmus; Marfan syndrome	Essentially negative	20% sickle cells; 20% ovalocytes; hemoglobin, 10.7 gm %; hematocrit, 35%; all other data within normal limits		
Daughter, 11, F	Poor muscular mass, de- creased subcutaneous fat, hyperextensible elbow, knee and finger joints, arachno- dactyly, winged scapulas, depressed anterior right hemithorax, gothic-arched palate, visual field defects; Marfan syndrome	Essentially negative	No sickling; 20% ovalocytes, hemoglobin, 10.5 gm. %; hematocrit, 38%; all other data within normal limits		
Son, 10, M Thin muscles, decreased subcutaneous fat, pigeon-breasted, hyperextensible fingers, arachnodactyly, ectopia lentis; height, 64.5 inches; span, 65 inches; Marfan syndrome		Normal growth up to age six after which he became thin	No sickling; hemoglobin, 10.8 gm. %; hematocrit, 35%; all other data normal		
Daughter, 8, F	Thin muscles, arachnodac- tyly, gothic-arched palate; Marfan syndrome	Essentially negative	40% sickle cells; hemoglobin, 10.2 gm. %; hematocrit, 39%; other data within normal limits		
Son, 5, M	Ectopia lentis, arachnodactyly; Marfan syndrome?	This patient was not used in this series			
Son, 2, M	Normal development thus far	This patient was n	not used in this series		

TABLE II
SERUM MUCOPROTEINS IN PATIENTS WITH THE MARFAN
SYNDROME AND IN CONTROL SUBJECTS

Group	Subjects (No.)	Mucoprotein (mg./100 ml.)	P
Control	22 6	96.0 ± 6.2* 65.0 ± 4.7	<0.05

* Standard error =
$$\sqrt{\frac{\Sigma(x-\bar{x})^2}{n(n-1)}}$$

are presented in Table II. It will be noted that the mean serum mucoprotein level in the control series was 96 ± 6.2 mg. per 100 ml., range 92 to 120 mg. per 100 ml. This value is based on observations in twenty-two subjects in good health; six were adult white males, and the remaining sixteen were Negro children ranging from six to fifteen years of age. There were seven males, and nine females in this group. There were no apparent differences between the mucoprotein levels in these groups, so that the mean of 96 ± 6.2 mg. per 100 ml. was obtained from pooled values. This value for normal human subjects is similar to that reported by Popper et al. [4] using the micromethod. Those authors also showed that when the samples are drawn in the morning, the values are not affected by diet or ordinary activity.

Table IV
RESPONSE OF SERUM MUCOPROTEIN LEVELS IN MARFAN
PATIENTS TO HIGH ASCORBIC ACID INTAKE

Treatment	Serum Mu (mg./1 seru	Change	
	Before	After	
Ascorbic acid, 400 gm.	88	60	
daily for six days	55	48	
	76	45	
	48	39	
Mean values	67	48	-29
No ascorbic acid sup-	76	74	
plements	84	85	
Mean values	80	80	0

Note: Ascorbic acid-treated subjects each received 400 mg. ascorbic acid daily for six days while they were on a regular diet. Group without ascorbic acid supplements received regular diet.

TABLE III
RESPONSE OF SERUM MUCOPROTEIN LEVELS IN NORMAL
SUBJECTS TO HIGH ASCORBIC ACID INTAKE

Treatment	Serum M (mg./	Change	
	Before	After	
Ascorbic acid, 400 mg.	84	78	
daily for six days	122	113	
	107	126	
	84	81	
Mean values	99	97	-2
No ascorbic acid sup-	84	91	
plements	98	96	
	84	83	
Mean values	92	90	-2

Note: Ascorbic acid-treated subjects each received 400 mg. ascorbic acid daily for six days while they were on a regular diet. Group without ascorbic acid supplements received regular diet.

The mean serum mucoprotein level in the patients with the Marfan syndrome was 65 ± 4.7 mg. per 100 ml. The difference between the control group and the Marfan group is statistically significant.

Response of Serum Mucoprotein Levels in Normal Subjects to Large Doses of Ascorbic Acid. Because ascorbic acid is known to stimulate fibroblast activity and the formation of connective tissue, it was decided to study the reaction of the mucoprotein levels to large oral doses of ascorbic acid. Three normal control subjects (white adults) were given 400 mg. ascorbic acid orally daily for six days. A comparable group was given no medi-

Table v
Changes in Serum mucoprotein levels following
SPONTANEOUS PNEUMOTHORAX IN A PATIENT WITH
THE MARFAN SYNDROME

Clinical Status		coprotein /100 ml.)
Resting level, no complaints On day of pneumothorax, two hours	76	
after pain	80	(+5%)
Day following pneumothorax	95	(+25%)
Four days following attack	115	(+51%)
Ten days after attack*		

* Patient was discharged on this day:

cation during this period. The serum levels of mucoproteins were determined in these patients at the end of this period. The data are presented in Table III. There was no significant change in the serum mucoprotein level following ascorbic acid ingestion.

Response of Serum Mucoprotein Levels in Patients with the Marfan Syndrome to Large Doses of Ascorbic Acid. Four of the subjects with Marfan syndrome were given 400 mg. ascorbic acid daily for six days. The remaining two patients received no medication. The serum mucoprotein levels are summarized in Table IV. There was no significant change in the patients who did not receive ascorbic acid, but in the patients with Marfan syndrome who received ascorbic acid there was a significant decrease (mean difference— 19 ± 6.2) in the serum mucoproteins.

Response of Serum Mucoprotein Level to Spontaneous Pneumothorax in a Patient with Marfan Syndrome. The serum mucoprotein level has been shown to be altered in occult degenerative processes and in the alarm reaction. The characteristic response in these situations is an increase in the serum mucoproteins. During the course of the present study the eldest child (K. H.), sixteen years of age, complained of acute pain in the right side of the chest, associated with shortness of breath. He was found to have absent breath sounds in the right hemithorax, with evidence of an effusion at the right base. Chest roentgenograms revealed a massive collapse of the right lung, and evidence of an effusion up to the ninth rib posteriorly. A low grade fever developed at this time. Thoracentesis revealed 1,500 ml. of sanguineous fluid; the patient tolerated the procedure well. Progress chest roentgenograms revealed gradual expansion of the right lung. A repeat thoracentesis two days later revealed 400 ml. of straw-colored fluid. After withdrawal of 500 ml. of air, progress x-ray films revealed almost complete expansion of the right lung. The patient was asymptomatic at discharge. Three weeks following discharge he was seen in the Emergency Room with acute pain in the right side of the chest. Physical examination was consistent with pneumothorax and effusion on the right. A roentgenogram of the chest confirmed the diagnosis and revealed a massive collapse of the right lung with an effusion up the eleventh rib posteriorly. The serum mucoprotein levels were studied during this second episode. Thoracentesis yielded 1,200 ml. of straw-colored fluid on the second day of

hospitalization. A chest x-ray film at this time revealed some re-expansion of the right lung. and considerable decrease of the effusion in the right base. Following the removal of an additional 150 ml. of fluid two days later, serial chest roentgenograms showed complete expansion of the lung. The patient was discharged on the tenth day following the pneumothorax.

The serum mucoprotein levels during the second episode are summarized in Table v. It will be noted that the level of mucoproteins rose following the pneumothorax with effusion, and returned to the resting level ten days later.

COMMENTS

The diagnosis of the Marfan syndrome was made in six of eight siblings. Two of these subjects also had evidence of sickle cell anemia, and one of ovalocytosis. The morphologic and clinical features in these patients were not suggestive of sickle cell disease, however. The remaining three patients in this group had no evidence of sickle cell disease. The mother, who was included in the control group, showed 4 per cent sickling of the erythrocytes. It was not possible to study the father or other relatives of these children. Further details of the hemoglobinopathy in these patients are being worked out. The findings reported in this paper cannot be ascribed to sickle cell disease, since the abnormal mucoprotein findings were also present in members without any evidence of sickle cell disease.

In this study the serum mucoproteins were shown to be lower than normal in patients with the Marfan syndrome. It was shown that the patient with Marfan syndrome is capable of responding with an increase in the mucoprotein levels following the insult of a spontaneous pneumothorax. The response of the patients with Marfan syndrome to ascorbic acid loading was quite different from that of control subjects. In the normal control subjects ascorbic acid loading resulted in no significant alteration in the serum mucoprotein levels whereas there was a decrease in the patients with Marfan syndrome following ingestion of ascorbic acid, possibly because the circulating mucoproteins were deposited in the tissues. The possibility that the ascorbic acid load caused a decreased mucoprotein synthesis seems unlikely since this vitamin is a powerful stimulant to fibroblast activity and connective tissue growth. The data are reminiscent of the lowered blood amino acid

levels following the injection of growth hormone. The decrease of amino acids following growth hormone administration is accompanied by an increase in protein synthesis [6]. Catchpole and co-workers [7] have shown an increase in the levels of other connective tissue constituents, e.g., glycoproteins, in ascorbic acid-deficiency. Presumably the increased glycoprotein levels in that situation are due to depolymerization of the ground substance [8].

Recent studies by Angevine et al. [9] have shown that in experimental lathyrism due to β -aminopropionitrile poisoning there are several features suggestive of a relationship to the Marfan syndrome. In animals with lathyrism due to the drug the skeletal and muscular development is abnormal; these animals die of ruptured aneurysms. Pathologic studies have demonstrated that the mucopolysaccharide content of the blood vessel walls in experimental lathyrism is increased. The increase in metachromasia in the tissues of rats given β -aminopropionitrile might be similar to the increase seen in ground substance undergoing depolymerization [7]. Whether or not this pattern obtains in the Marfan syndrome is not known.

In spite of the low level of serum mucoproteins in the patient with Marfan syndrome, there is a marked response to the insult of pneumohemothorax, and to ascorbic acid loading. In the former circumstance, there is a connective tissue response indicated by an increase in serum mucoprotein level; in the latter, a decrease.

SUMMARY

The resting levels of serum mucoproteins in the patients with Marfan syndrome were found to be lower than those of control subjects. The mucoprotein level in the patient with Marfan syndrome decreased following the ingestion of large amounts of ascorbic acid, but was not altered in control subjects. The serum mucoproteins rose following spontaneous pneumothorax in a patient with the Marfan syndrome.

The findings are discussed in relation to the underlying error(s) in connective tissue metabolism in the Marfan syndrome.

Acknowledgment: I would like to acknowledge the help of Sister Margaret Albert, Supervisor of the Outpatient Department in follow-up of the patients. Doctor Kenneth L. McCoy, Director of Laboratories, made available facilities for this study.

REFERENCES

 McKusick, V. The heritable disorders of connective tissues. J. Chron. Dis., 2: 609, 1956.

 Macleod, M. and Williams, A. W. The cardiovascular lesions in Marfan's Syndrome. Arch. Path., 61: 143, 1956.

Moehlio, R. C. Arachnodactyly (Marfan's Syndrome). Am. J. Roentgenol., 61: 797, 1949.

 De la Huerga, J., Dubin, A., Kushner, D. S., Dyniewicz, H. and Popper, H. Studies on serum mucoprotein (Seromucoid). I. Turbidimetric method. J. Lab. & Clin. Med., 47: 403, 1956. II. Physiologic variations and response to stress. J. Lab. & Clin. Med., 47: 409, 1956.

 WINZLER, R. J., DEVOR, A. W., MEHL, J. W. and SMYTH, I. M. Studies on the mucoproteins of human plasma. I. Determination and isolation. J.

Clin. Invest., 27: 609, 1948.

 Russell, J. A. and Capiello, M. The effects of pituitary growth hormone on the metabolism of administered amino acids in nephrectomized rats. *Endocrinology*, 44: 333, 1949.

 PIRANI, C. L. and CATCHPOLE, H. R. Serum glycoproteins in experimental scurvy. Arch. Path., 51: 597,

1951

 GERSH, I. and CATCHPOLE, H. R. The organization of ground substance and basement membrane and its significance in tissue injury, disease, and growth. Am. J. Anal., 85: 457, 1949.

 CHURCHILL, D. W., GELFANT, S., LALICH, J. and ANGEVINE, D. M. Alterations in the polysaccharide and elastic fibers in the aortas of rats fed toxic lathyrus factor. Lab. Invest., 4: 1, 1955.

Transitory Congenital Neutropenia: A New Syndrome*

Report of Two Cases

MARIO STEFANINI, M.D., TROSE H. MELE, B.S. and DAVID SKINNER, M.D.

Boston, Massachusetts

Newton Lower Falls, Massachusetts

NEUTROPENIA is not too rarely seen in the immediate postporture immediate postpartum period. It is attributed to a number of mechanisms such as septicemia [1,2], allergic reactions to the proteins of maternal blood [3] and the like. In the first instance the bone marrow is poor in myelogenous cells; in the second, maturation arrest of the granulocytic series is outstanding. In all reported cases, neutropenia was first noted between the third and ninth day of life and regressed quickly. There is no evidence that any of these cases exhibited neutropenia at birth. Congenital neutropenia, on the other hand, is extremely rare. Careful search of the literature failed to disclose a well documented instance. A newborn whose blood showed mild leukopenia at birth has been described by Browaeys and Pley [4]. The child's mother was suffering from aplastic anemia, possibly due to intoxication with organic arsenic administered for the treatment of syphilis. The child was delivered by cesarean section immediately after the mother's death, and was stillborn. The many complicating features make this case one of doubtful significance.

We describe in this article two cases of congenital, transient neutropenia in newborn infants of neutropenic mothers. In one case neutropenia was due to the transplacental transmission of a neutropenic factor; the mechanism operating in the other case could not be identified. These cases may be examples of a hitherto unrecognized syndrome.

METHODS OF STUDY

Preparation of White Cells for Agglutination Studies. Blood was obtained from an ante-

cubital vein of the mother. Puncture of the femoral or jugular veins was used when large amounts of blood were needed from the newborn. Suspensions of white cells were prepared as described by Dausset et al. [5].

Precipitin Reaction. This test was performed as described by Kabat and Mayer [6]. White cell suspensions were prepared from normal donors as described by Dausset et al. [5]. A few drops of 0.1 per cent acetic acid solution and, thirty seconds later, saline solution (one-third the volume of the original blood used) was added to the final suspension of white cells to obtain complete lysis of the erythrocytes remaining in the preparation. White cells were then separated by centrifugation at 2,500 r.p.m. at 4°c. for ten minutes, a process repeated three times after resuspending the white cell button each time with the same volume of saline solution. Final preparations were then lyophilized in the cold under 29 inches of vacuum, and the lyophilized material was stored at -20°c. until used. At the time of testing a solution was prepared containing 20 mg. of leukocyte powder in physiological saline solution. Solution of the material was aided by adding 2 ml. of ether to each 10 ml. of volume and allowing the ether to evaporate in the cold. The solution (representing the antigen) was then diluted to obtain scalar concentrations through 20, 15, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.0625 mg. per cent. The serum tested was also diluted serially with physiological saline solution from 1/25 to 1/12,800. Reacting mixtures contained 0.1 of serum and 0.1 of antigen, at crossing solutions.

Complement Fixation. A minor modification of the technic outlined by Kolmer [7] was used.

^{*} From the Joseph S. Stanton Memorial Laboratories; the Department of Pathology, Newton-Wellesley Hospital; and the Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts. Supported by grant-in-aid H-2131 from the National Institutes of Health. Presented at the Annual Meeting of the American Federation for Clinical Research, Atlantic City, New Jersey, May 1957.

[†] Established Investigator, American Heart Association.

Fresh white cells prepared as described by Dausset et al. [5] represented the antigen. The antigenic suspension was the yield of white cells from 40 ml. of group O Rh positive normal human blood, in a volume of 3 ml. of saline solution (average white blood cell count of 15,000/cu. mm.).

Antihuman Globulin Absorption Test. The technic was as described in the original publications of Moulinier [8], and Steffen and Schindler [9].

Injection of Serum from Persons with Leukopenia into Normal Persons. One pint of blood was collected by gravity in plastic bags containing ACD solution. Plasma was separated by centrifugation at 3,000 r.p.m. at 4°c. for thirty minutes and transferred by gentle pressure to another plastic bag. The average yield was 180 to 240 ml. Within four hours of collection, the plasma was injected at a speed of forty drops/minute into normal volunteers. White cell and differential counts were taken prior to and at various intervals of time up to ten days following the transfusion.

Injection of Serum from Patients with Leukopenia into Normal Rabbits. Patients' whole blood was collected in sterile glass test tubes. It was allowed to clot and incubated at 37°c. for one hour. It was then centrifuged at 3,000 r.p.m. for ten minutes at room temperature. The separated serum was transferred to sterile test tubes, and stored at -20° c. unless immediately used. When needed, the serum was thawed slowly in an icebox at 4°c., filtered through paper and injected into the marginal vein of the ear through a 25-gauge needle. Blood for counts was collected from the central artery of the ear through a 25-gauge needle into a tuberculin syringe containing 0.4 ml. of 0.1 M solution of sodium citrate. The blood was aspirated until the solution reached the volume of 1 ml. The mixture was then transferred to a glass test tube.

The Effect of the Hemolytic Fraction of Splenic Tissue on Normal and Patients' White Cells. Xefteris and Stefanini [10] have isolated from human spleen a lipidic fraction which hemolyzes normal human red cells. Such fraction was prepared from the splenic tissue of both patients, dried under vacuum and, when used, redissolved in barbital buffer of pH 7.5. Two-tenths milliliter of a suspension of normal white cells prepared with Dausset's technic was incubated at 37°c. for thirty minutes with an equal volume of saline solution containing 1 unit of hemolytic fraction. After various periods of incubation

white cells were counted and their morphology studied under phase microscopy at a magnification of 960 times.

Preparation of Splenic Tissue Fractions. Three aliquots of 50 gm. of washed spleen from the two patients with leukopenia were weighed, the capsule removed by blunt dissection and tissue minced. The thin slices obtained were transferred to round-bottom centrifuge tubes of 40 ml. capacity. Approximately 20 ml. of cold normal saline solution was added. Tissue was pressed to remove most of the blood, centrifuged at 3,000 r.p.m. for fifteen minutes and the supernatant discarded. This process was repeated at least six times or until the supernatant fluid was clear of blood, all steps being carried out at a temperature of 4°c.

Preparation of a saline extract: Blood-free splenic tissue was transferred to a small mortar and 5 ml. of normal saline solution added. The tissue was ground finely, the pulp transferred to another test tube and centrifuged at 3,000 r.p.m. for fifteen minutes. The supernatant was removed and the extraction repeated with another portion of 5 ml. of saline. The two eluates were combined and frozen until used.

Preparation of an alcohol-ether extract: Blood-free splenic tissue was ground in mortar after adding 5 ml. of alcohol-ether mixture.* After grinding, the liquid phase was separated by slow centrifugation (500 r.p.m. for two minutes) and the supernatant was removed. Extraction was repeated and the extracts were pooled.

Preparation of acetone and benzene extracts: Splenic tissue was extracted with similar technic, using 2 aliquots of 5 ml. of acetone or benzene.

Injection of Splenic Extracts into Rabbits. extracts were filtered through glass wool and then were dried under vacuum in the cold. The dry extracts were kept at -20° c. under an atmosphere of nitrogen. At the moment of use, each extract was shaken thoroughly with 5 ml. of phosphate buffer at pH 7.2. Ether, acetone and benzene extracts had a very milky, turbid appearance. Prior to injection they were again filtered through glass wool. Two milliliters of each fraction (equivalent to 10 gm. of original splenic tissue) were injected through a 25-gauge needle into the marginal vein of the ear of albino rabbits of an average weight of 6 pounds. No reaction was observed to any of the injections. Blood was drawn from the central artery

^{* 96.5} ml. of ethyl ether were added to 3.5 ml. of 95 per cent ethanol.

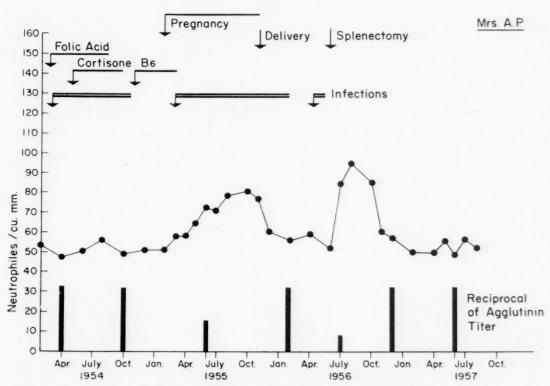


Fig. 1. A graphic history of patient A. P. (Case 1).

of the ear as described. White cell and differential counts were obtained before injections and at various intervals afterwards. Smears were stained by Wright's method.

Paper Electrophoresis of Serum. This was carried out as described by Block and co-workers [11]. Staining of proteins and glycoproteins was carried out according to Block et al. [11] and Koĭw and Grönwall [12], respectively.

Adrenalin Test. This was performed as described by Chatterjea et al. [13].

CASE REPORTS

CASE I. A. P., a twenty-three year old married woman, was referred to us for evaluation of chronic leukopenia. (Fig. 1.) The patient had suffered from scarlet fever at the age of five. Chronic multiple infections had become evident when she was twentyone, and were controlled by occasional use of antibiotics. On physical examination, the gums were moderately hyperplastic; boils were present in various skin areas. Lymph nodes, liver and spleen were not palpable. Urinalysis was negative. Serum fasting blood sugar, non-protein nitrogen, uric acid and creatinine were 103, 28, 4.1 and 2.2 mg. per cent, respectively. Blood count revealed the following: red blood cell count, 4.12 million/cu. mm.; hemoglobin, 13.1 gm. per cent; hematocrit, 42 per cent; white blood cell count, 1,800/cu. mm.; platelets, 275,000/ cu. mm. (direct method); and reticulocytes, 0.4 per

cent. The differential count showed 3 neutrophils, 3 eosinophils, 1 basophil, 87 lymphocytes, 5 monocytes and 1 Türk cell. The morphology of all cellular elements was normal. The electrophoretic pattern of

TABLE I
DIFFERENTIAL BONE MARROW COUNT IN THE PATIENTS
STUDIED (PERCENTAGE FIGURES)

	A. P.	A. P. Baby	M.R.	M. R. Baby
Unclassified cells	0.2	1.5	0.1	1.3
Myeloblasts	2.3	0.7	2.0	0.9
Promyelocytes:			1	-
Neutrophils	4.2	3.9	5.1	4.1
Eosinophils	0.1	0.3	0.2	0.2
Basophils	0.1	0.1	0.1	0.1
Myelocytes:				
Neutrophils	39.4	45.2	36.1	35.9
Eosinophils	2.5	3.2	1.55	4.1
Basophils	0.7	0.1	0.8	0.2
Metamyelocytes:				
Neutrophils	17.2	7.3	14.2	10.7
Eosinophils	0.4	0.1	0.7	0.9
Basophils	0	0	0	0.1
Segmented:				
Neutrophils	2.7	8.1	2.9	6.3
Eosinophils	0.3	0.1	0.4	0.1
Basophils	0	0	0.1	0
Proerythroblasts	0.1	0.2 -	0.3	0.3
Erythroblasts	5.2	0.9	6.1	1.2
Normoblasts	13.8	24.3	14.3	25.2
Megakaryoblasts	0.1		0.2	0.1
Megakaryocytes	0.4	0.15	0.3	0.2
Reticuloendothelial cells	0.9	0.2	1.4	0.3
Monocytes	0.7	0.3	1.0	0.9
Lymphocytes	12.5	4.2	11.9	7.6
Plasma cells	0.2	0.15	0.35	0.2

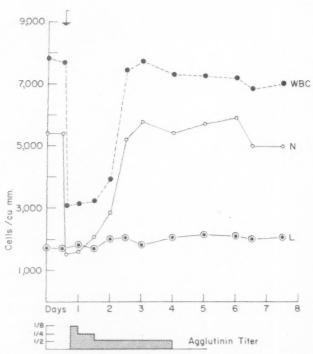


Fig. 2. The leukopenic effect of patient A. P.'s plasma injected into a healthy person. Note the prompt neutropenic effect, suggesting immediate disposal of circulating neutrophils by the leuko-agglutinin; and the short survival of the transferred leuko-agglutinin. Bone marrow appeared inhibited in the first twenty-four hours and hyperactive afterwards, thus perhaps explaining the restoration of neutrophils to normal values within seventy-two hours. WBC = white blood cells; N = neutrophils; L = lymphocytes.

serum proteins and the electrophoretic distribution of carbohydrates were normal. Bone marrow specimens collected from the sternum and from the iliac crest were hypercellular. Megakaryocytes were normal in number and activity; erythroid series was normal. The granulocytic series was grossly hyperplastic with evident maturation arrest. (Table 1.) Tests for lupus erythematosus were uniformly negative, using direct [14], indirect [15] and a slide [16] technic. Blood type was A₁, Rh₁, Rh₂ (CDE). A splenic puncture was carried out through the intercostal approach [17]. Material was aspirated through a 20-gauge needle; it contained lymphoblasts, lymphocytes and reticulum cells in the expected proportion [17].

A preliminary leukocyte agglutination test by the technic of Dausset indicated that the inactivated patient's serum clumped normal white cells at a titer of 1:32. Buffy coat preparations from the patient's blood were observed directly under phase microscopy. Within one to three minutes neutrophils formed large clumps surrounded by platelets.*

Other immunologic tests were performed to establish

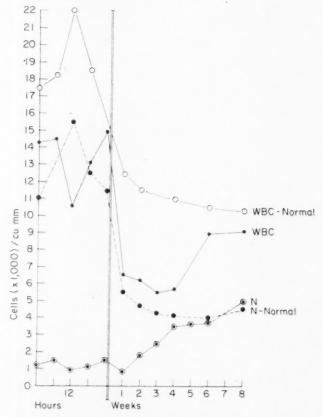


Fig. 3. Absolute count of leukocytes and neutrophils in the child of patient A. P. (Case I) followed up for eight weeks after birth. Values were essentially similar in the newborn of patient M. R. (Case II).

the significance and specificity of these findings. The patient's serum agglutinated 67 per cent of samples of white cells tested, including those of her husband. The agglutinating factor (? iso-antibody) was active over wide ranges of temperature (20°c. to 50°c.) and pH (4.6 to 8.8); it was stable on storage at -20° c. and was not removed by absorption of serum with barium sulfate. The gamma globulin fraction was eluted after electrophoretic migration of the patient's serum. It agglutinated normal white cells at a titer of 1:2, while other electrophoretic fractions were inactive. No red cell or platelet antibodies were detected by standard technics in the patient's serum. Experiments in vivo were also carried out. Five hundred milliliters of the patient's blood was collected in a plastic bag containing ACD solution. The plastic bag was centrifuged at 3,000 r.p.m. for thirty minutes to obtain separation of all cellular elements. The plasma was separated and injected into a normal person of a compatible red cell group. A severe neutropenia developed in the recipient which lasted two and a half days. (Fig. 2.) The serum of the recipient agglutinated most samples of normal white cells for a period of four days, including his own collected prior to the administration of the leukopenic serum. The bone marrow taken twenty-four hours after the injection

^{*} Eight to ten minutes' time are needed to observe a similar phenomenon with normal buffy coat.

Table II

Adrenalin test in two patients with idiopathic leukopenia*

	Time (min.)						
	0	5	15	30	60	90	
Patient A. P.:							
Red blood cell count (million/cu. mm.)	3.98	4.27	4.55	4.02	3.87	3.90	
Hemoglobin (gm. %)	11.9	12.7	12.5	12.0	11.6	11.8	
White blood cell count (thousand/cu. mm.)	1.98	3.4	3.8	4.7	4.5	4.2	
Neutrophils	0.24	0.27	0.27	0.47	0.58	0.59	
Eosinophils			0.04	0.12			
Basophils			0.07	0.05			
Lymphocytes	1.38	1.94	1.87	3.10	2.92	2.60	
Monocytes	0.38	1.19	1.25	0.92	0.99	1.0	
Platelets (× 1,000/cu. mm.)	287	292	317	350	270	275	
Reticulocytes (%)	0.4	1.3	1.0	0.7	0.6	0.2	
Patient M. R.:							
Red blood cell count (million/cu. mm.)	4.38	4.68	4.72	4.74	5.09	4.57	
Hemoglobin (gm. %)	14.1	15.0	14.9	15.1	15.3	14.2	
White blood cell count (thousand/cu. mm.)	1.75	3.2	4.6	5.15	4.3	4.0	
Neutrophils	0.31	0.26	0.32	0.56	0.65	0.68	
Eosinophils	0.03	0.03	0.14	0.03	0.08	0.08	
Basophils			0.09	0.05			
Lymphocytes	1.09	1.9	3.22	3.72	2.19	2.13	
Monocytes	0.37	0.7	0.83	0.87	1.2	1.08	

^{*} Basic counts showed neutrophil counts higher than usual in both cases (? effect of expectancy or fear). Although there was some rise in neutrophils and a temporary rise in eosinophils, most of the increments were of lymphocytes and monocytes. Responses were essentially similar in both patients. Results probably indicated poor "neutrophil reserve"; thus, they tended to exclude the spleen as the pathogenic mechanism of neutropenia, a hypothesis proved to be correct by the failure of splenectomy in both cases.

was indistinguishable from that of the donor. Thus, the patient's serum contained an agent (? iso-antibody) which could be transferred to a normal recipient and was capable of: (1) agglutinating normal leukocytes; and (2) depressing the maturation of the myelogenous series in the bone marrow. Two days later, although a leuko-agglutinin was still demonstrable in the recipient serum, his bone marrow had become hyperplastic and rich in mature granulocytic cells. Thus, the immediate neutropenia was probably due to the effect of the transfused agglutinin in the recipient's leukocytes; the fairly prompt return to normal values was due to the response of the bone marrow after an initial inhibition of maturation by the transfused leuko-agglutinin.

The patient was treated with folic acid, cortisone and pyridoxine hydrochloride. A course of nitrogen mustard was also given with some trepidation in the attempt to decrease the leuko-agglutinin titer. The neutropenia became extremely severe, requiring continued antibiotic therapy for seven weeks.

The patient's first pregnancy occurred during the eleventh month of observation. The pregnancy was uneventful but her gums became grossly hyperplastic

and fungating. The leuko-agglutinin titer seemed slightly decreased and the neutrophil count rose slightly. Continuous antibiotic therapy was given during pregnancy. Delivery of a normal female occurred uneventfully on November 4, 1955. The infant's blood was identical with that of the mother. The child was born with severe neutropenia which persisted for three weeks. The neutrophil count gradually rose, reaching a plateau near normal values the fourth week of life. (Fig. 3.) A bone marrow specimen was collected from the child's left tibial shaft on the third day of life. Preparation showed hyperplasia of the granulocytic series with maturation arrest. (Table 1.) On the thirtieth day after birth the bone marrow showed regression of the maturation arrest of the myelogenous series and return to normal findings for this age of life. It was possible to obtain samples of venous blood from the femoral vein every few days. A leukocyte agglutinin with a titer of 1:32 was present at birth. Leukocytes from the mother's buffy coat were agglutinated by the child's serum. The titer decreased slowly, no agglutination being noted with the serum collected on the fifteenth day of life. White cells were obtained from the child on the

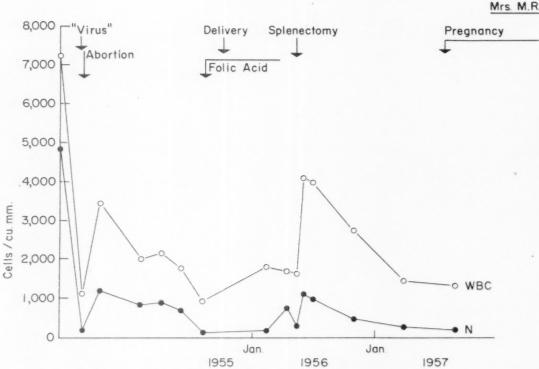


Fig. 4. A graphic summary of the history of patient M. R. (Case II.)

thirtieth day of life. These were agglutinated by the mother's and child's serum obtained at birth at a titer of 1:64 and 1:32, respectively.

Six months after birth of the child the mother was still severely leukopenic and the leuko-agglutinin titer was unmodified. Results of the adrenalin test (Table II) were equivocal. In view of the failure of all forms of treatment employed, splenectomy was advised and was performed in August 1955 by Dr. John W. Spellman of Saint Elizabeth's Hospital. The organ weighed 190 gm. Microscopic section showed reticuloendothelial hyperplasia. No agglutinins or leukolysins were obtained from the patient's spleen by our technics. A saline extract of the splenic tissue was examined by paper electrophoresis [18]. The various fractions were then eluted, the agglutinin being recovered only from the area of the gamma globulins. Negative results were obtained with extracts from spleens of two normal persons (autopsy material) and from two patients with idiopathic thrombocytopenic purpura. The white cell and neutrophil count rose for a short period of time only following surgery. The appearance of the bone marrow and the leukoagglutinin titer were unmodified by splenectomy. It is of interest that no infection developed following splenectomy up to September 1957, when the patient left this area. No further evidence of underlying disease had developed. The child appears entirely normal.

CASE II. M. R., a twenty-nine year old housewife, mother of two children, ages six and four, was re-

ferred to us for the evaluation of severe leukopenia during pregnancy. A third pregnancy had been terminated by abortion one year previously, perhaps due to a severe infection in the upper respiratory tract. When first seen on August 5, 1955, the patient was seven months pregnant. White blood cell count had been normal twelve months prior to the abortion when severe leukopenia had first been noted. Since that time the white blood cell count had oscillated between maximum and minimum figures of 4,000 and 1,000/cu. mm., respectively, with severe constant neutropenia. (Fig. 4.) Physical examination showed evidence of pregnancy. Gums were reddened and fungating. (Fig. 5.) Blood count gave the following results: red blood cells, 3.21 million/cu. mm.; hemoglobin, 10.8 gm. per cent; hematocrit, 34 per cent; white blood cells, 950/cu. mm. with 4 myelocytes, 4 metamyelocytes, 12 monocytes and 80 lymphocytes. Platelets were 220,000/cu. mm. (direct method) and the erythrocyte sedimentation rate 40 mm./one hour (Westergren). Blood type was O, Rh₁ (CDe). Bone marrow obtained from the sternum (Table 1) was hypercellular. Megakaryocytes were also abundant and active, and the erythroid series was normal. Granulocytic series was hyperplastic, with definite arrest of maturation. Electrophoretic studies of the patient's serum revealed an increase in α and β globulin fractions, and minor changes in the glycoproteins, usually associated with pregnancy [19]. (Fig. 6.) The test for lupus erythematosus was negative. The patient received Folvite® (5 mg. three times a day) and oral penicillin (600,000 units daily) during the rest of her



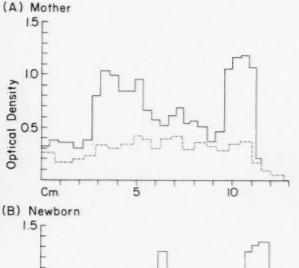
Fig. 5. The gums in patient M. R. (Gums of patient A. P. had a similar appearance.)

pregnancy which was uneventful. We were able to examine the patient's parents and her two children. They were healthy, their white cells and differential counts were normal, and their serums did not contain demonstrable leukocyte agglutinins.

Extensive attempts were made to demonstrate antileukocyte factors in the patient's serum. Tests of agglutination, lysis, precipitation, complement fixation and anti-human globulin consumption gave consistently negative results. *In vivo* tests were equally disappointing. The injection of 250 ml. of the patient's plasma into a normal person did not induce leukopenia over a period of fifteen days following the transfusion. The bone marrow of the recipient, aspirated one day and five days after the infusion, appeared normal. The injection of the patient's plasma or serum into rabbits was not followed early or late by changes in the neutrophil counts of greater magnitude than that caused by normal serums.

Delivery occurred on October 27, 1955. The child was severely neutropenic at birth. Normal values were reached at four weeks of age after a slow rise, similar to that found in Case I. (Fig. 3.) The child's blood type was O, Rh₁ (CDe); thus, there was no obvious red cell incompatibility between mother and child. Bone marrow at birth showed myeloid hyperplasia and, one month later, appeared entirely normal according to age. The child's serum did not exhibit agglutinins against normal or white cells or those of the mother. The electrophoretic migration of proteins and glycoproteins showed increase in the α_2 and β protein fractions. Glycoproteins, on the other hand, appeared increased in the α_1 and albumin fractions. (Fig. 6.) Such findings are usual in the newborn.

The mother's neutrophil count rose slightly after delivery. In February 1956, however, the white blood cell count was again 1,800/cu. mm. with 10 neutrophils, 13 eosinophils and 5 basophils. An adrenalin test was performed at this time which



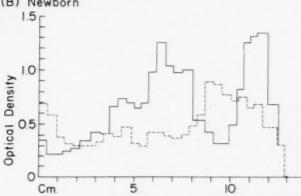


Fig. 6. The electrophoretic pattern in patient M. R. and M. R.'s newborn: proteins and glycoprotein (direct scanning). Note (1) mother's serum: increase of the α and β fractions (pregnancy); (2) newborn infant's serum: high α_2 and β fractions, and high content of carbohydrate-containing protein preferentially migrating with the albumin fractions.

induced a slight rise in the total white and neutrophil count, and a significant one in the number of lymphocytes and monocytes. (Table II.) Bone marrow specimens aspirated before and during the test showed a numerical increase of mature neutrophils after administration of adrenalin. These results could not be interpreted easily. Splenectomy, however, seemed advisable since the patient had failed to respond, as in Case 1, to treatment with folic acid, ACTH, cortisone, prednisone and pyridoxine. This procedure was performed on May 4, 1956, by Dr. Richard I. Smith of Newton-Wellesley Hospital. Total and differential white cell counts in the capillary blood were taken at different times during the procedure; counts were also made on samples of blood from the splenic artery and vein. (Table III.) The ligation of the splenic pedicle was followed by a sudden but temporary increase in the number of circulating band forms and mature neutrophils. The blood from the splenic artery contained many monocytes as compared to the venous blood which, in turn, was richer in lymphocytes. The spleen weighed 284 gm. The cut surface was smooth and homogenous with faint follicular and trabecular markings. Microscopic sections showed

TABLE III
BLOOD COUNTS IN RELATION TO SPLENECTOMY IN PATIENT M. R.*

Blood Counts	One Hour before Surgery	After Anes- thesia	Incision of Skin	Pedicle Ligated	End of Surgery	One Hour after Surgery	Splenic Vein	Splenic
Red blood cell count (million/cu.								
mm.)	4.48	4.62	4.23	4.15	4.02	4.30	4.53	4.42
Hemoglobin (gm. %)	13.8	13.9	12.7	12.1	11.9	12.3		
White blood cell count (thousand/cu.								
mm.)	1.78	1.9	2.03	2.97	3.70	4.3	1.87	1.93
Band forms	0.04	0.09	0.04	0.03	0.66	2.28		0.09
Neutrophils	0.32	0.04	0.18	0.06	0.74	0.95	0.12	0.13
Eosinophils	0.14	0.19	0.12	0.3	0.19	0.04	0.13	0.26
Basophils	0.02	0.02		0.03			0.06	0.02
Lymphocytes	0.72	1.01	1.24	2.01	1.55	0.98	1.46	1.10
Monocytes	0.52	0.41	0.42	0.42	0.51	0.48	0.13	0.28
Histiocytes		0.02		0.15	0.04			0.04
Platelets (X 1,000/cu. mm.)	272	302	309	254	297	364	302	315

Note: (1) the outpouring of neutrophil cells after splenectomy; (2) the increase in number of lymphocytes during surgery, with return to near preoperative level after splenectomy; (3) the predominance of monocytes in the splenic artery as compared to the splenic vein blood.

* No blood transfusion was needed during surgery.

that the sinusoids were dilated and relatively empty. Fibrous tissue was moderately increased in the red pulp where scattered groups of eosinophils were present. Malpighian corpuscles contained groups of reticuloendothelial cells. There were occasional megakaryocytes. The final diagnosis was reticuloendothelial hyperplasia of the spleen. No primary disease was noted.

Rabbits were injected with various fractions of the patient's splenic tissue. Similar extracts were obtained from the splenic tissue of patients with other hematological disorders and from normal persons in whom the spleen had been accidentally removed at surgery. There was no occurrence of leukopenia or neutropenia.

Leukopenia recurred a few months after surgery. Tests for lupus erythematosus have remained negative. From a clinical viewpoint, however, the patient feels stronger. She no longer suffers from frequent infections, and there has been regression of the hyperplasia of the gums. The child has thus far been entirely normal. Mother and child were last examined in August 1957.

The patient was delivered of a second child in March 1958. The child was born with neutropenia. The neutropenia was observed and disappeared in the same time as in the first child born before splenectomy was performed in the mother.

COMMENTS

Neutropenia is a complex syndrome due to multiple mechanisms. (Table IV.) In an increas-

ing number of cases it appears related to the presence of factors in the patient's blood which are able to agglutinate or lyse circulating neutrophils as well as to inhibit the maturation of the granulocytic cells, as shown by findings in the bone marrow [20]. It is generally assumed that the demonstration of a neutropenic factor in the patient's blood indicates an immune mechanism and these cases are accordingly considered instances of "immune neutropenia." In the absence of experimental work of the type which has clearly established the immunologic nature of antiplatelet factors in some thrombocytopenic states [21,22], the identification of a circulating neutropenic factor as an antibody is little more than suggestive, although possible. Since protein factors as well as antibodies may pass from mother to fetus under special conditions (related to their properties, to the status of the placenta and the like), it is not surprising that neutropenic children may be born to neutropenic mothers. It should not be concluded, however, that the presence of a demonstrable leukopenic factor in the mother's blood is necessarily followed by its passage through the placenta and by the birth of neutropenic children. We have observed two additional patients with immune neutropenia probably due to a demonstrable circulating leuko-agglutinin who

TABLE IV

A PATHOGENETIC CLASSIFICATION OF NEUTROPENIA

I. Congenital

- A. Bone marrow failure: part of Fanconi's syndrome or one of its variants
- B. Transplacental transfer of a neutropenic factor from mother (? immune): transitory; transfer of drugs
- C. Idiopathic

II. Neonatal

- A. Severe viral and bacterial infections after birth
- B. ? Allergic mechanisms

III. Acquired (adults)

- A. Decreased production of neutrophils by the bone marrow
 - Aplasia or obliteration of the bone marrow (myelosclerosis, myelofibrosis, metastatic neoplasms, leukemias, aplasia [radiation effect, toxic effect, drug effect*])
- B. Increased destruction of neutrophils at the periphery
 - ? Hypersplenism: † Felty's syndrome, portal hypertension, congestive splenomegaly, primary diseases involving the spleen
 - 2. Immune mechanisms† (leuko-agglutinins and leukolysins)
 - a. Drug-induced* (aminopyrine, Butazolidin,® hydantoin, sulfonamides, etc.)
 - Following infections (viral: viral pneumonias, cat scratch fever, infectious mononucleosis, etc.;
 bacterial)
 - c. In collagen diseases
 - d. Idiopathic (? autoimmunization)

* Drugs may directly depress formation of neutrophils by the bone marrow, or increase their peripheral destruction through immune mechanisms.

† Both mechanisms may also inhibit maturation or delivery of granulocytic cells in and from the bone marrow. Whether "hypersplenism" might also act through immune mechanisms is uncertain at present.

have delivered normal children. Of particular interest is one of these cases in which the mother has twice delivered children with normal white cell and differential counts at birth. As in Case 1, the titer of the patient's leuko-agglutinin remained essentially unmodified during both pregnancies.

The demonstration of a neutropenic factor within the patient's blood was complete in one of the two cases studied. Some of the properties suggested that this factor might be an antibody [23]. The clinical and laboratory features of the second patient were essentially similar, yet no leukopenic factor could be demonstrated in her serum. The negative result of our experiments cannot, of course, be taken to indicate that no such factor might have been present, since all investigators agree that technics for the detection of antileukocyte factors are rudimentary at best. The failure to demonstrate a leukopenic factor in in vivo experiments is also of limited significance because of the considerable dilution which follows the infusion of a small volume of the patient's plasma into the blood stream of a normal recipient. The very fact that the patient's child was born neutropenic suggests the presence in the mother's blood of a factor able to pass through the placental filter. The spleen appeared to have no role in the production of the

leukocyte antibodies in this patient because of the negligible effect of splenectomy. This conclusion was confirmed by the fact that a second child was born with neutropenia after the spleen had been removed.

Our studies failed to indicate the mechanism and site of production of the leukopenic factor in patient A. P. The patient had never received blood transfusions; she had not suffered from infectious or viral diseases prior to the onset of neutropenia. There was no evidence of primary disease known to be associated with the appearance of leukocyte antibodies (collagen diseases and the like) and no further clinical findings have developed since our observation. The child was born of the mother's first pregnancy. Thus, the neutropenic factor was truly idiopathic, at least to the limit of our knowledge. Splenectomy had a negligible and temporary effect on the neutropenia. Thus, the spleen had a minor role, if any, in the elaboration of the neutropenic factor. All forms of therapy tried, both with the purpose of improving the bone marrow's maturation arrest and to decrease the production of antibodies, failed.

A last observation of significance is that the occurrence of infections in our patients decreased after splenectomy, notwithstanding the persistence of severe neutropenia. Perhaps splenectomy

eliminated one of the mechanisms of final destruction of the neutrophils damaged by the leuko-agglutination, allowing their longer survival and thereby improved protection against infections.

SUMMARY

1. Two cases of transitory congenital neutropenia are described. In both instances neutropenia most likely was due to the transplacental

passage of a neutropenic factor.

2. Both patients exhibited similar clinical and laboratory findings. The bone marrow in the leukopenic mothers as well as in the newborn infants showed hyperplasia and maturation arrest of the granulocytic series. In one case, however, the mother's serum contained a demonstrable leuko-agglutinin which could be transferred by transfusion to a normal person. The factor exhibited many characteristics of an antibody. No neutropenic factor was demonstrable in the mother in Case II. The neutropenia and the titer of the leukocyte agglutinin were unaffected by splenectomy.

3. The two cases herein reported represent examples of a syndrome apparently not previ-

ously described.

Acknowledgment: We wish to thank Dr. John Malloy Flynn, Boston, Massachusetts, for referring Case I and Dr. R. E. Sylvester, Auburndale, Massachusetts, for the opportunity of studying Case II.

REFERENCES

- SLOBODY, L. B., ABRAMSON, H. and LOIZEAUX, L. S. Agranulocytosis of the newborn infant. J. A. M. A., 142: 25–26, 1950.
- Schümer, L. Agranulozytose beim Neugeborenen. Arch. Kinderh., 147: 164–169, 1953.
- Lehndorff, H. Transitorische Granulocytopenia beim Neugeborenen. Helvet. paediat. acta, 6: 173– 183, 1951.
- Browaeys, J. and Pley, J. Hématologie d'un prématuré agranulocytose maternelle. Sang, 21: 826–829, 1950.
- DAUSSET, J., NENNA, A. and BRECY, H. Leukoagglutininins. v. Leukoagglutinins in chronic idiopathic or symptomatic pancytopenia and in paroxysmal hemoglobinuria. *Blood*, 9: 696-720, 1954.
- Kabat, E. A. and Mayer, M. M. Experimental Immunochemistry, pp. 20–66. Springfield, Ill., 1948. Charles C Thomas.
- 7. Todd, J. C. and Sanford, A. H. Clinical Diagnosis

by Laboratory Methods, p. 802. Philadelphia, 1948. W. B. Saunders Co.

MOULINIER, J. Technique de la réaction de consommation d'antiglobuline. Rev. franç. d'études clin. et

biol., 1: 355-364, 1956.

 Steffen, C. and Schindler, H. Bericht über die Verwendung des Antihumanglobulin—Ablenkungsversuches für der Nachweis eines Antileukozyten—Antikörpers bei Agranulozytosen. Münch. med. Wchnschr., 97: 469–471, 1955.

 XEFTERIS, E. and STEFANINI, M. Tissue hemolytic system of lipidic nature in man. Fed. Proc., 16: 378,

1957.

- Block, R. J., Durrum, E. L. and Zweig, G. A Manual of Paper Chromatography and Paper Electrophoresis, pp. 406–408. New York, 1955. Academic Press, Inc.
- Koĭw, E. and Grönwall, A. Staining of proteinbound carbohydrates after electrophoresis of serum on filter paper. Scandinav. J. Clin. & Lab. Invest., 4: 244–246, 1952.
- Chatterjea, J. B., Dameshek, W. and Stefanini, M. The adrenalin (epinephrine) test as applied to hematologic disorders. *Blood*, 8: 211–235, 1953.
- LEE, S. L. A simple test for L.E. cells. Am. J. Clin. Path., 21: 492-496, 1951.
- KURNICK, N. B., SCHWARTZ, L. I., PARISER, S. and LEE, S. L. A specific inhibitor for human desoxyribonuclease and an inhibitor of the lupus erythematosus cell phenomenon from leucocytes. *J. Clin. Invest.*, 32: 193–201, 1953.

 SNAPPER, I. and NATHAN, D. J. Mechanisms of L.E. cell phenomenon studied with a simplified test.

Blood, 10: 718-729, 1955.

17. Moeschlin, S. Spleen Puncture. London, 1951.

W. Heinemann.

18. Moschides, E., Stefanini, M., Magalini, S. and Kistner, S. A. The "mucoprotein fraction" (phosphotungstic acid precipitate) in tissue and serum: a comparison of normal findings and findings in leukemia and lymphoma. J. Lab. & Clin. Med., 50: 216–224, 1957.

 SHETLAR, M. R., KELLY, K. H., FOSTER, J. W., SHETLAR, C. L. and EVERETT, M. R. Serum polysaccharide levels in pregnancy, parturition and post-partum state. Am. J. Obst. & Gynec., 59:

1140-1145, 1950.

 MOESCHLIN, S. Immunoleucopénies et immunogranulocytoses. Rev. hémat., 8: 249–262, 1953.

- KISTNER, S. A. and STEFANINI, M. Studies on platelets. XVII. An experimental study of the development of platelet antibodies. J. Lab. & Clin. Med., 48: 846–865, 1956.
- STEFANINI, M. and MELE, R. H. The significance of platelet antibodies. The vi Congress of the European Society of Hematology. Copenhagen, August 1957.
- STEFANINI, M., CHATTERJEA, J. B., DAMESHEK, W., ADELSON, E. and MEDNICOFF, I. B. Studies on platelets. IX. Observation on the properties and mechanism of action of a potent platelet agglutinin detected in the serum of a patient with idiopathic thrombocytopenic purpura. *Blood*, 8: 26– 64, 1953.

Echinococcus Disease in the United States*

ARNOLD M. KATZ, M.D. and CHIA-TUNG PAN, M.D.

Bethesda, Maryland

Boston, Massachusetts

CASE of echinococcus infection in the United A States is usually regarded as a medical curiosity. Of the eleven newly diagnosed cases at the Massachusetts General Hospital in the past decade, six were presented at clinicopathological conferences and published as Cabot cases. Few physicians in this country have a wide experience with this disease and no review of its occurrence here has appeared in the North American literature since 1941 [1]. However, there is no indication that echinococcosis is disappearing from this country. The present report reviews some of the features of this disease as seen in the United States and the first native case from the State of Massachusetts is reported. The natural history and epidemiology of the parasite are reviewed, the clinical picture is discussed briefly, and some simple but infrequently stressed laboratory diagnostic methods are described.

Echinococcus infection was probably known to Hippocrates [2,3]. The parasitic nature of the disease was suspected in the 17th century by Francesco Redi and the life history of the parasite was described by Naunyn in 1863 [4,5]. Virchow described the alveolar form of the disease in man in 1855 [6], and the adult worm developing from the alveolar hydatid was obtained from a dog in 1901 (cited by Vogel [7]). Although many of the pioneer investigators were aware of two different disease pictures produced by echinococcus parasites, it was only recently that two species of tapeworm, E. granulosus and E. multilocularis were demonstrated to cause the different pathological effects. The disease is now recognized throughout the world, and in some countries up to 15 per cent of the autopsies on human beings have revealed echinococcus infection [8].

The first North American case of echinococcus disease was reported in 1822 [9]. Since then several reviews of the cases reported from the

United States and Canada have appeared [1,9–13]. When Magath [13] last reviewed the North American literature, he included 596 cases from these two countries reported up to 1948. In most of these cases the patients were immigrants from countries in which the disease was endemic and in only thirty were the infections considered to be contracted in the United States (native or autochthonous cases).

Echinococcus Infection as Seen in the United States. The present series includes 556 cases diagnosed in the United States and consists of 479 cases summarized up to 1948 [1,9–13], thirty-six cases published since then [14–35], and forty-one cases from the Massachusetts General Hospital not included in previous summaries.

It is impossible to be certain of the time and place of infection in this chronic disease and most of the infections are assumed to have been brought to this country from endemic areas. The probable geographical origins of infection are summarized in Table 1. The largest proportion of the recent cases came from Italy, Greece and Eastern Europe; fifty years ago there were relatively more cases from Iceland, the British Isles and Germany. This change probably reflects both a decline in the incidence of echinococcosis in the latter countries and a changing pattern of immigration to the United States. Thirty-eight of these patients probably acquired the infection in the United States although this fact is unequivocally established in only twentyeight of the case reports.

The number of published cases of echinococcus infection has declined considerably during the first quarter of this century. (Fig. 1.) Since 1926 reports of new cases have been appearing at a rate of about fifty each decade. The age distribution of the recent cases is similar to that of twenty years ago [13]. The number of native cases reported per decade has remained at an

^{*} From The Medical Services, Massachusetts General Hospital, and the Department of Tropical Public Health, Harvard School of Public Health, Boston, Massachusetts.

TABLE I

THE PRESUMED GEOGRAPHICAL ORIGINS OF THE CASES OF ECHINOCOCCOSIS REPORTED FROM THE UNITED STATES (1822–1956) AND THOSE SEEN AT THE MASSACHUSETTS GENERAL HOSPITAL (M. G. H.) (1856–1956)

Presumed Origin of Infection	1	es from J. S. A.	Cases from the M. G. H.	
	No.	%	No.	%
United States	38	6.8	-1	1.3
Italy and Sicily,	118	21.2	30	38.0
Greece.,	78	14.0	21	26.6
Germany and Austria	44	7.9	2	2.5
Russia, Poland and Baltic States	28	5.0	5	6.3
British Isles	27	4.9	6	7.6
Asia Minor	19	3.4	5	6.3
Central and South America	16	2.9	1	1.3
Iceland	11	2.0	2	2.5
Balkan Countries	10	1.8	2	2.5
Spain and Portugal	9	1.6	0	0
France	8	1.4	1	1.3
Scandinavia	4	0.7	1	1.3
Asia	2	0.4	0	0
Australia and New Zealand	2	0.4	1	1.3
Africa	1	0.2	0	0
Not known	141	25.4	1*	1.3
Total	556		79	

^{*} This man was a sailor who had traveled all over the world.

average rate of about six since the first was described in 1900. (Fig. 1.) It has now been established that autochthonous infections have occurred in fourteen states. (Fig. 2.) Since most

of the reported cases have come from large medical centers in the more populous states, no valid conclusions can be drawn from the distribution of this disease in the United States except that it has been encountered in almost every state. (Fig. 2.)

A tabulation of the anatomic locations of the hydatid cysts in cases from the United States is presented in Table II. While there may be inaccuracies because of the varied sources of the data, both in time and place, and because of the paucity of autopsy cases, certain observations seem valid. The liver was by far the most commonly affected organ, and in almost two-thirds of the cases this was the only organ to contain a hydatid cyst. Infections involving a distant organ along with the liver were uncommon, occurring in fewer than 10 per cent of patients with hepatic cysts. However, one-fifth to onethird of hydatids in organs other than the liver were accompanied by distant cysts; thus extrahepatic infection was more likely to be multiple.

The frequencies of organ involvement reported here are almost identical to those reported by Dévé who in 1913 reviewed 2,727 published cases [35], and Arce who in 1941 reviewed his experiences in Argentina [37]. Dévé in 1917 (cited by Dew [4]) found multiple cysts in 28 per cent of 115 cases and Dew in 1928 estimated that "multiple infestations occur in at

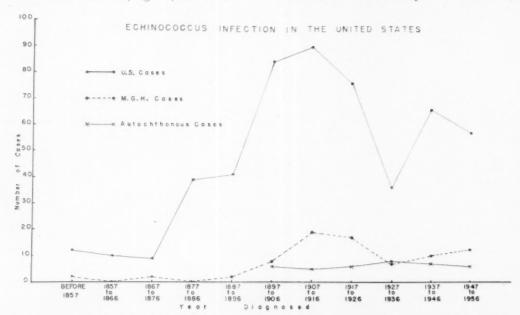


Fig. 1. Echinococcus infection in the United States. The distribution of reported cases by decades of hydatid infection is plotted along with that of cases seen at the Massachusetts General Hospital and autochthonous cases. The dates of diagnosis for thirty-six of the United States cases are not known and, therefore, are omitted from the graph. Discussed in text.

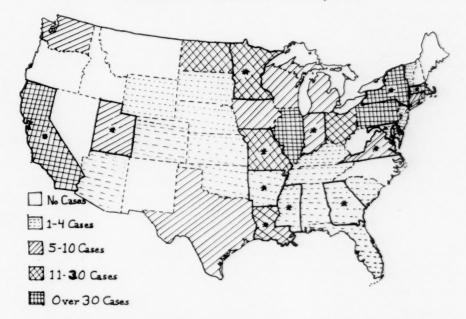


Fig. 2. The geographical distribution of echinococcus infection in the United States. The geographical distribution of the 556 cases of hydatid infection seen in the United States is plotted on this map. Each case has been assigned to the state from which it was reported. (Six cases were omitted because it was impossible to determine the states in which the cases were seen.) The fourteen states with documented native cases are bordered with a solid line and marked with an asterisk. Discussed in text.

least 60 per cent of cases" [4]. In the present series involvement of more than one organ occurred in 10 per cent of cases. However, Dévé and Dew included multiple cysts in a single organ as cases of multiple infection.

Echinococcus Infection as Seen at the Massachusetts General Hospital. Seventy-nine cases of echinococcosis have been collected from the records of the Massachusetts General Hospital. These make up 15 per cent of the total cases reported from the United States. Since these cases include all that were catalogued in the files of the Department of Pathology and the Record Room, they make up a more uniform series than those collected from the literature. The only basis for inclusion in this group was parasitological proof of the diagnosis and therefore several patients, with cysts observed on x-ray film and positive skin tests, were omitted. The first documented case seen here dates back to 1856 although some cases seen before 1875 may have been overlooked due to inadequate cataloguing of older records. It was possible to obtain the age, birthplace, date of diagnosis and the location of the cysts in every case and complete case summaries were lacking in fewer than ten cases. The series includes fourteen* autopsy

* One of these autopsies was limited to the abdomen.

cases. Of the seventy-nine cases, forty-four have already been described in the literature [38–53].

The presumed geographical origins of these infections are similar to those of the published cases from the United States except that there is only one apparent native case. (Table 1.) Furthermore, the incidence of echinococcosis at this hospital parallels the incidence derived from the reported cases. (Fig. 1.)

The anatomic distribution of the cysts in the Massachusetts General Hospital series is similar to that in the reported cases from the United States. (Table II.) Isolated hepatic involvement was the commonest form of the disease; half of the seventy-nine patients manifested this alone and in the fourteen autopsy cases, eight patients had infection only of the liver. Of the seventy-nine patients, 70 per cent had involvement of a single organ as did 64 per cent of those who came to autopsy. This autopsy series is too small to permit other conclusions but it seems fair to conclude from the experience here that the presence of more than one cyst is most likely with extrahepatic infection.

With one exception, all these cases were of unilocular hydatids. This exception was a man who had spent many years in a Russian prison camp during World War II in whom a liver

TABLE II

THE ANATOMIC LOCATIONS OF ECHINOCOCCUS CYSTS IN PATIENTS REPORTED FROM THE UNITED STATES (1822–1956) AND THOSE SEEN AT THE MASSACHUSETTS GENERAL HOSPITAL (1856–1956)

	Cases from the United States Cases fro			n the Massachusetts General Hospital			
Organs Involved	27 (544)*		Entire Se	eries (79)†	Autopsy (Cases (14)†	
	No. (541)*	%	No.	%	No.	% .	
Liver (total)	. 402	74	57	72	12	86	
Liver alone	. 360	67	40	51	8	57	
Liver and peritoneum	. 17	3	13	17	1	7	
Liver and distant organ	. 25	5	4	5	3	21	
Peritoneum (total)		9	19	24	3	21	
Peritoneum and distant organ	. 12	2	2	3	1	7	
Lung (total)		10	5	6	1	7	
Lung and distant organ	. 15	3	4	5	1	7	
Spleen (total)		3	2 .	3	1	7	
Spleen and distant organ		1	1	1	1	7	
Kidney (total),		4	4	5	0	0	
Kidney and distant organ	. 4	0.7	1	1	0	0	
Body wall (muscle, etc.) (total)		3	9	11	1	7	
Body wall and distant organ		1	5	6	1	7	
Bone (total)		2	2	3	0 .	0	
Bone and distant organ		0.4	1	1	0	0	
Bladder (total)		1	0	0	0	0	
Bladder and distant organ		0.4	0	0	0	0	
Pleura (total)		2	2	3	0	0	
Pleura and distant organ	2	0.4	1	1	0	0	
Breast		1	0	0	0	0	
Brain		1	1	1	1	7	
Spinal cord		0.2	0	0	Ô	0	
Prostate		0.4	0	0	0	0	
Heart		0.4	1	1	1	7	
Eye		0.2	0	0	0	0	
		0.2	0	0	0	0	
Ovary Uterus		0.2	0	0	0	0	

* In an additional fifteen cases the exact location of the cysts is not known. These cases were omitted from the total cases in the table.

† These figures represent total patients.

biopsy in 1956 demonstrated multilocular (alveolar) echinococcosis.

The mean age of the Massachusetts General Hospital cases is increasing and is now close to fifty whereas it was near thirty-five in 1900.

CASE REPORT

To our knowledge the following is the first case of echinococcus infection in a person who has always lived in Massachusetts. Aspects of this case have been published in transcriptions from conferences held at this hospital [48,49] but the

social history is presented here in full for the first time.

Mrs. DiM. (MGH No. 534902) is a forty-four year old housewife living in Revere, Massachusetts, a suburb of Boston. She was born in Boston and has never lived outside the Boston area although she took three short trips out of Massachusetts. Two of these were to a suburb of New York City, each for a week in 1925 and 1940; the other was an auto trip through Quebec in 1950, after the radiological demonstration of her hydatid cyst. Mrs. DiM. remembers having owned two dogs, both of them given to her by neighbors who had raised them from puppies. She has

never lived in a rural neighborhood, and the nature of her exposure has not been determined.

The patient was first seen at the Massachusetts General Hospital in 1946. At that time she complained of pain in her left thigh dating back to 1940. X-ray films showed a mass which had partially destroyed the left wing of the ilium protruding into the pelvis as a calcified cyst. A chest roentgenogram showed a density in the lower right lung field. Two calcified ring shadows in the upper right quadrant of the abdomen were believed to be gallstones (the patient later had a typical attack of cholecystitis and a cholecystogram showed a non-filling gallbladder). A needle biopsy specimen of the mass in the hip revealed only skeletal muscle but a large amount of clear fluid drained from the puncture wound. A tentative diagnosis of metastatic sarcoma of the ileum was made at this time and she was given 1,600 r to the left hip. However, she failed to keep an appointment for open biopsy and was lost to follow-up for five

Mrs. DiM. was next seen here in November 1951. One week before admission a tender mass had appeared in her left buttock, and she was admitted to another hospital where an intravenous pyelogram showed a mass compressing the left ureter. She was referred to the Massachusetts General Hospital where she presented with a large, tender, fluctuant mass overlying the left ilium posteriorly. Anteriorly, a mass was palpable deep in the lower left quadrant of the abdomen. Her temperature was 102.4°F, and white blood count was 17,700 per cu. mm. with 81 per cent neutrophils and no eosinophils. Roentgenograms of the pelvis showed a large increase in the size of both the area of bone destruction and the calcified cyst. A chest film showed several new round densities in each lung.

Following a course of penicillin and streptomycin the abscess was opened and was found to communicate with the ilium. A grape-like cyst, 6 mm. in diameter, was found in the pus which flowed out of the incision. On microscopic examination the cyst had a laminated, acellular membrane consistent with that of an echinococcus cyst. The result of the Casoni intradermal test, performed with cyst fluid, was negative. For several weeks large amounts of pus containing similar cysts drained from the wound and the patient continued to have a spiking fever. A month after admission the abscess was epened anteriorly again draining large quantities of pus and many cysts. In spite of this operation the patient's condition did not improve and two weeks later a third exploration of the left hip was performed through a large incision which connected the earlier anterior and posterior drainage incisions. Almost every tissue cut through contained cysts. Some in the gluteal muscle were 5 cm. in diameter and one of the larger cysts contained daughter cysts; no hooklets or scolices were seen. The entire wing of the left ilium was removed



Fig. 3. Diagnostic material from hydatid cysts. A single hooklet recovered from the sputum of our case (Mrs. DiM.). Original magnification × 1,500. Wet mount. (Reprinted from American Practitioner and Digest of Treatment, 7: 746, 1956.)

but the stump of bone left behind was riddled with cysts.

The patient felt better after this third operation but her temperature remained elevated and the wound continued to drain. Roentgenograms of the pelvis showed persistent sequestration, and the possibility of hindquarter amputation was raised. The patient flatly refused to consider this, and her doctors agreed that this radical procedure offered little chance of a cure. Accordingly, she was discharged to a convalescent hospital four months after admission.

Four months after arriving at the convalescent hospital, Mrs. DiM. walked out on crutches. Her wound continued to drain and she occasionally had fever although she felt generally better. A year after discharge she was walking with a cane and had resumed most of her normal activities.

Mrs. DiM's. most recent admission to the Massachusetts General Hospital was in December 1955. For four weeks she had been troubled by pleuritic pain in the left side of the chest associated with a non-productive cough and evening fevers with temperatures to 102°F. The morning of admission she had a particularly violent bout of coughing and suddenly began to raise large amounts of bloody sputum. Her chest pain was immediately relieved but she came to the hospital badly frightened and still bringing up sputum.

Physical examination revealed a chronically ill woman. The rectal temperature was 100°F. There were signs of consolidation in the upper left lung field and dullness at the base of the left lung. The scar on her hip was well healed with the exception of two small draining sinuses. Her hemoglobin was 9.8 gm. per cent and white blood count was 22,200 per cu. mm. with 68 per cent neutrophils and 7 per cent eosinophils. The sputum was odorless, tenacious, colorless but streaked with blood. Microscopic

examination and culture revealed a mixed bacterial flora, and Wright's stained sputum contained many polymorphonuclear cells of which about a third were eosinophils. Chest roentgenograms showed consolidation of the upper left lobe with a radiolucent area 4 cm. in diameter in the consolidated area corresponding in position to the largest density seen four years before. The other previously noted densities were unchanged. A hooklet (Fig. 3) found in a concentrated specimen of the sputum on the second hospital day confirmed the clinical impression of ruptured pulmonary echinococcus cyst.

Following treatment with penicillin the patient's temperature fell and production of sputum ceased. The effusion at the base of the left lung cleared and râles were heard for the first time over the upper left lobe although signs of consolidation persisted. On the tenth hospital day she was discharged to rest at home.

Over the two years since discharge her clinical state has steadily improved. There has been no return of pulmonary symptoms and roentgenograms show fibrosis of the upper left lobe with a slowly shrinking cavity. Her hip still drains and occasionally troubles her but there has been no change evident on x-ray examination. Now, eleven years after the discovery of her hydatid infection, Mrs. DiM. is managing her household and is gaining so much weight that she is planning to diet.

COMMENT

Since echinococcosis is seen so infrequently in the United States a few of the salient features of the disease will be reviewed here. Much of this material is covered in standard textbooks of parasitology and an excellent clinical review is found in a book written thirty years ago by

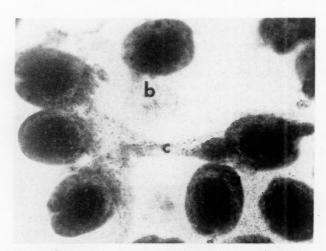


Fig. 4. Diagnostic material from hydatid cysts. Scolices from a unilocular cyst of a human liver; a, scolex; b, a group of hooklets in a degenerated scolex; c, germinative membrane. Hematoxylin-azure II-eosin stain, original magnification \times 250.

Dew in Australia [4]. Some newly discovered aspects of the natural history of the parasite are presented herein and particular emphasis is placed on diagnostic technics which have been somewhat slighted in the recent American literature.

Life Cycle and Epidemiology. Man is infected by the larval form of echinococcus, never by the adult tapeworm which is found in the intestine of a variety of canine hosts. E. granulosus was, until recently, the only recognized species. However, it has been shown, largely through the recent studies of Rausch et al. [54-57] and Vogel [7], that two long recognized disease pictures are produced by separate species of parasite. The more common unilocular hydatid cyst is caused by E. granulosus while the alveolar cyst is the larval form of E. multilocularis. The life cycles of the two species are similar but there are differences in the morphology of the adult tapeworm and hydatids, and in their natural host ranges.

The adult parasite is a tapeworm of only several millimeters, having usually four segments, which lives in the small intestine of the definitive hosts: dogs, wolves, foxes and other canines. When the gravid terminal segment of the tapeworm bursts, either in situ or after becoming detached, ova are discharged into the intestinal contents of the host. The mode of infection of the intermediate host (including man) thus depends on fecal contamination of food, fingers and (rarely) water [4,37]. The ingested ova hatch in the small intestine of the intermediate host and the liberated embryos penetrate the intestinal mucosa to reach the circulation. From here they are carried to the liver and other organs in which they may lodge and may develop into hydatid cysts. Many organs and tissues of the human body are susceptible to echinococcus infection although the host reaction may destroy the parasite in its early stages of development [4,58]. In an established unilocular cyst, small larvae (scolices) grow within the cyst from buds, or brood capsules, arising from the inner germinative membrane. (Fig. 4.) Daughter cysts may develop from dislodged scolices or bits of the germinative membrane, usually after trauma. The daughter cysts in turn may form scolices and both can give rise to new hydatid cysts if released into the tissues of the intermediate host [4,54,59]. In the case of E. multilocularis, the larva attains an alveolar form by the rapid exogenous formation of cysts which

invade the host tissues like a malignant tumor [54]. (Fig. 5.) Distant metastases are believed possible in disseminated cases of both forms of infection, and it is likely that the case reported here exemplifies such an occurrence.

When the definitive host ingests hydatid material in the raw viscera of an intermediate host, sexually mature tapeworms develop in the intestine from the scolices and the life cycle is completed.

There are two life cycles of E. granulosus, one involving domestic animals, the other wild animals. In countries such as Australia, Argentina and Greece in which there is extensive grazing, sheep and cattle usually serve as the intermediate hosts and dogs as the definitive host. In North America a sylvatic cycle is carried on by moose, deer, caribou, etc. as the intermediate hosts, and wolves, coyotes and, rarely, dogs as the definitive hosts [60,61].

Alveolar hydatid disease has been seen in many parts of the world but is most common in central Europe, Siberia and Alaska. The definitive hosts for E. multilocularis are foxes and dogs while the natural intermediate hosts include several species of small insect-eating rodents. Foxes are the more important definitive hosts since they rely on these rodents for food [7,56].

Clinical Diagnosis. The diagnosis in a case of an intact hydatid cyst is extremely difficult. Symptoms other than those due to a space-occupying tumor are usually absent. Since growth of the parasite is very slow, several decades may pass before the disease becomes clinically manifest [4]. The cyst can remain dormant and asymptomatic for the life of the host but in some cases cysts reach amazing sizes. The "colossal" cyst reported by Barnett contained over 11 gallons of fluid (cited by Carmalt-Jones [62]). Occasionally a distinctive "hydatid thrill" may be felt over the cyst after it is balloted. This has been described as an "exquisite spring-like vibration which is quite distinctly prolonged beyond the moment of percussion and which is associated with a remarkable drum-like resonance heard on auscultation" [62]. When a cyst is located in a vital organ like the brain, it may cause symptoms early in its development [4], while in other cases the cyst may first come to notice at the time of rupture or secondary bacterial infection.

Complications in older hydatid cysts are frequent. Rupture is common and usually follows

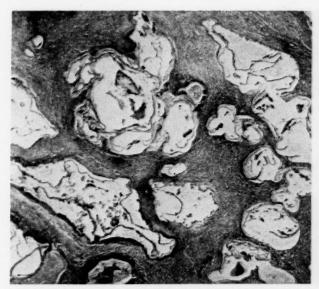


Fig. 5. Diagnostic material from hydatid cysts. Alveolar hydatid cysts from a human liver. Hematoxylin and eosin stain, original magnification × 40.

trauma or attempts at surgical removal. Internal rupture often proves fatal. Immediate death probably results from an anaphylactic reaction to the antigenic cyst fluid [63,64]; later deaths are usually due to dissemination of infective scolices with subsequent production of multiple cysts. Rupture into the pleura may cause hydrothorax, hydropneumothorax or empyema while rupture of an hepatic cyst can cause bile peritonitis. Not infrequently hepatic cysts rupture through the diaphragm into the pleura or even the lung [4]. Recovery is more common in cases of rupture to the outside, for example, through a bronchus, the bile ducts or ureter. Anaphylactic shock can follow rupture into the lungs. The gradual shedding of daughter cysts following rupture of a renal cyst can cause renal colic and similarly gallbladder colic has followed rupture of an hepatic cyst into the biliary system [4,22]. Secondary bacterial infection is a common complication after rupture and may destroy the parasite, leaving a chronic abscess in place of the cyst. (This probably occurred in the case herein reported.) Slow leakage of cyst fluid into the surrounding tissues can cause urticaria, pruritus and eosinophilia [4,62]. However, the eosinophilia is usually mild; about half of all patients have over 300 eosinophils per cu. mm. and only about a third have over 500 eosinophils per cu.

The classic radiological finding in this disease is a cyst with a thinly calcified wall. However, calcification is not always seen and pulmonary

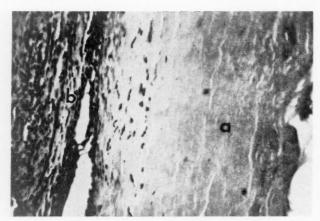


Fig. 6. Laminated membrane (a) and adventitia (b) from the wall of a unilocular cyst. Hematoxylin-azure II-eosin stain, original magnification × 250.

cysts are rarely calcified. The diagnosis is rarely made by x-ray studies alone although there may be distinctive radiological findings in cases of partially ruptured renal or pulmonary cysts [66–68].

Immunologic Diagnosis. The two immunologic tests commonly used in the diagnosis of echinococcosis are the intradermal (Casoni) and the complement fixation test. The Casoni test consists of an intradermal injection of a hydatid antigen. Hydatid cyst fluid is usually used, but good results have been reported when the antigen consists of extracts of larval echinococcus elements, or even other species of tapeworm [56,69–71]. A positive reaction appears as a large wheal, often with pseudopods, surrounded by a zone of erythema. This usually develops in a few minutes, reaches a peak in about fifteen minutes and fades in an hour. In some cases a delayed reaction is seen. The latter is an area of induration and erythema which develops twelve to twenty-four hours after injection and fades after about seventy-two hours [65]. Between 75 and 92 per cent positive reactions are seen in proved cases [37,65,72,73]. False positive reactions are probably infrequent although control data are lacking for some types of antigens. They have been reported in patients with advanced carcinomatosis, kala-azar and taeniasis other than echinococcosis [74].

The complement fixation test, while more specific than the intradermal test, is less sensitive, giving 50 to 60 per cent positive results in proved cases [37,65,75]. False negative results are obtained usually with degenerated or simple hydatid cysts, especially simple cysts of the lung [4]. False positives probably occur but the

frequency is not known with certainty since most of the reports are from endemic areas and the absence of exposure to this disease is hard to establish.

The intradermal reaction can usually be obtained many years after successful removal of a solitary cyst while the complement fixation test is reported to become negative in a few months [4,65,74]. If the complement fixation test remains positive, the presence of another cyst must be strongly suspected. When the diagnosis of echinococcosis is considered, both tests should be employed; however, positive reactions do not establish the diagnosis.

Skin tests and complement fixation tests at the Massachusetts General Hospital have yielded the expected proportion of positive results. Nine of fourteen skin tests (64 per cent) and eighteen of twenty-one complement fixation tests (86 per cent) were positive; several of the latter became negative after a solitary hydatid cyst was removed.

Parasitological Diagnosis. A definite diagnosis of echinococcosis depends on the recovery and identification of hydatid elements from biopsy specimens or body discharges. Hepatic cysts may rupture into the bile ducts and grape-like cysts or pieces of bile-stained laminated membrane may be found in the feces [65]. Cysts in the kidney may discharge hooklets and scolices into the urine [65,66] while the contents of a ruptured lung cyst are usually brought up in a watery sputum.

With experience hydatid elements can be readily identified. The contents of unilocular cysts usually contain a large number of hooklets, scolices and fragments of laminated and germinative membrane. (Figs. 3, 4 and 6.) Any material believed to contain cyst fluid should be centrifuged and the sediment examined microscopically for hooklets and scolices. Hooklets (Fig. 3. and Fig. 4B) are refractile objects about 20 microns in length and can be found under low magnification (X 100) after some practice. They can be recognized easily under higher magnification (X 400). Scolices are ovoid in shape when they are invaginated in the cyst membrane and measure about 120 by 85 microns. Around the anterior end of each scolex is a row of hooklets, which may resemble a mop when the scolex is evaginated. An intact daughter cyst may resemble a grape while bits of laminated membrane look like curled up grape skins. These can sometimes be found in washed

feces by simple sedimentation. Fragments believed to be laminated membrane should be soaked in saline and teased apart; if they are truly bits of hydatid element, their edges will show lamination on microscopic examination. (Fig. 6.) Sputum may be examined directly, but in cases in which there is much mucus or pus, the sputum should be digested with an equal volume of 4 per cent aqueous sodium hydroxide for one to two hours at 37°c. The digested material is then centrifuged for five minutes at 2,000 r.p.m. in a table model centrifuge (325 X g) and the sediment examined microscopically. (This was the technic used to recover the hooklet in the case reported here.) Since alveolar cysts in man produce few scolices, the diagnosis usually depends on identification of the laminated membrane in tissue sections. (Fig. 5.)

Even with these technics a definite diagnosis may not be possible before operation. However, because of the special surgical technics needed to handle these cysts, it is important to try to make the diagnosis preoperatively.

Treatment. It is generally believed that hydatid cysts should be removed whenever possible. The incidence of complications in untreated cases is high although small calcified cysts may remain asymptomatic for the life of the patient and large cysts may be found incidentally at autopsy. There is no accepted medical treatment for this disease; chemotherapy has not been beneficial and x-ray therapy has proved ineffective. Subjective improvement has been reported to follow multiple injections of echinococcus antigen [76,77]. However, this therapy is not generally accepted and some proponents believe that surgical treatment is to be preferred when it is possible [77]. Furthermore, injections of cyst fluid are potentially dangerous since anaphylaxis may follow even small injections of antigen. Aspiration of the cyst, once commonly performed as a therapeutic as well as a diagnostic measure has fallen into disrepute because of the serious danger of infection or dissemination of the cyst fluid. Thus operative removal or marsupialization remains the treatment of choice. The surgical technics are varied and depend on the location and condition of the cyst; the reader is referred for details to several excellent reviews from clinics with wide experience in the management of this disease [64,65,68,78-85].

Public Health Aspects. In spite of the rarity of documented native human cases of echino-

coccosis, there is good evidence that this disease is established in the United States. The present prevalence of hepatic infection of cattle in this country is at least 0.01 per cent. Between 1950 and 1956, when 20 to 25 million cattle and calves were slaughtered, the livers from 2,648 were rejected because of the presence of echinococcus cysts [87]. In spite of this relatively high figure, canine infection in the United States is very rare. Natural infection of dogs has been noted only in Georgia, Tennessee, Kentucky, Mississippi and the District of Columbia, with a total of nine cases reported [88]. No evidence of echinococcosis has been found on routine stool examinations of several thousand dogs examined annually at the Angell Memorial Animal Hospital in Boston. Furthermore, routine autopsies numbering 300 to 400 each year have failed to disclose this parasite [89]. There seems to be little danger of exposure of dogs to this disease since the current sanitary methods of animal slaughter do not provide an opportunity for dogs to ingest the viscera of domestic animals; furthermore it is the practice to destroy stray dogs in most communities.

A large reservoir of echinococcosis has recently been discovered in the wild-life of Northwestern Canada [90] and Alaska [91]. The impact of this reservoir on the human population of that region is profound, with several hundred new cases reported from Northwestern Canada in the past decade [61,92,93]. In addition, 31 per cent of over 2,000 natives tested had a positive Casoni reaction [94]. This constitutes a potential health hazard for the population of the United States since both the infected wolf and moose may range into the United States, and a dog brought from the endemic area may spread thousands of infective ova in an American community. However, at present there is no evidence that this disease is becoming an important public health problem in the United States.

SUMMARY

- 1. Published case reports of echinococcus disease in the United States have appeared at a rate of about five new cases annually. An average of one new case is diagnosed each year at the Massachusetts General Hospital.
- 2. Most of the cases seen in this country have been in immigrants and only thirty-eight of the 556 cases noted at the time of writing can be considered to be native cases. These native

cases have come from fourteen states and have appeared at a rate of about six each decade since 1900. The first native case from Massachusetts is

recorded and described in this report.

3. An echinococcus cyst may be found in any organ of the body, in the present series, as in others, most often in the liver. When found in this organ, fewer than 10 per cent were accompanied by cysts in distant organs. Hydatid infection of other organs, while less common, was associated with distantly located cysts in 20 to 35 per cent of cases. Of all patients only 10 per cent had cysts in more than one organ.

4. It has recently been shown that the two clinical forms of this disease are caused by different species of the parasite. The unilocular cyst is caused by E. granulosus and the invasive alveolar cyst is produced by E. multilocularis.

5. The manifestations of intact, alveolar, infected, partially ruptured and acutely ruptured cysts are different, and clinical diagnosis is often difficult. The Casoni skin test and the complement fixation test increase the accuracy of diagnosis but cannot be counted on either to rule in or to rule out the disease. Definite diagnosis requires recovery and identification of the parasitic elements. This is difficult, often impossible.

6. Although there is a newly discovered reservoir of echinococcosis in Northwestern Canada and the prevalence of hepatic infection of cattle in the United States is about 0.01 per cent, it does not appear that this disease is becoming a public health problem in the United States.

Acknowledgment: The authors would like to express their indebtedness to the many members of the Medical and Surgical Services and Department of Pathology of the Massachusetts General Hospital who helped to locate case histories. We would also like to thank Drs. Walter Bauer, Morton Swartz and Lloyd Smith, of the Massachusetts General Hospital, and Drs. Thomas H. Weller and Donald L. Augustine, of the Department of Tropical Public Health, Harvard School of Public Health, for their helpful criticism of the manuscript.

Figures 3, 4, 5 and 6 were photographed from the collection of teaching specimens in the Department of Tropical Public Health, Harvard School of Public Health. All specimens were prepared by Dr. Chia-tung Pan except the specimen used for Figure 5, which was sent to the department through the courtesy of Dr. Robert Rausch, Arctic Health Research Center, U. S. Public Health Service, Anchorage, Alaska.

REFERENCES

 MAGATH, T. B. Hydatid (echinococcus) disease in North America. Pennsylvania M. J., 44: 813, 1941.

 ADAMS, F. The Genuine Works of Hippocrates, p. 770. London, 1849. The Sydenham Society.

3. Jones, W. H. S. Hippocrates, vol. 4, p. 203. London, 1931. William Heinemann Ltd.

Dew, H. R. Hydatid Disease. Its Pathology, Diagnosis and Treatment. Sydney, 1928. The Australasian Medical Publishing Co. Ltd.

 NAUNYN, B. G. J. Ueber die zu Echinococcus hominis gehoerige Taenie. Arch. Anat., Physiol. u. wissensch. Med., p. 412, 1863.

 VIRCHOW, R. Die multiloculaere, ulcerirende Echinokokkengeschwulst der Leber. Verhandl. Phys.-Med. Gesellsch. Wuerzburg, 6: 84, 1855.

- VOGEL, H. Ueber den Entwicklungszyklus und die Artzugehoerigkeit des europaeischen Alveolarechinococcus. Deutsch. med. Wehnschr., 80: 931, 1955.
- Dungal, N. Echinococcus in Iceland. Am. J. M. Sc., 212: 12, 1946.
- Lyon, I. P. A review of echinococcus disease in North America. Am. J. M. Sc., 123: 124, 1902.
- MAGATH, T. B. Echinococcus disease: etiology and laboratory aids to diagnosis. M. Clin. North America, 5: 549, 1921.
- MAGATH, T. B. Hydatid (echinococcus) disease in Canada and United States. Am. J. Hyg., 25: 107, 1937.
- MAGATH, T. B. The epidemiology of hydatid (echinococcus) disease in Canada and the United States. Arch. Int. de la Hidatid., 5: 55, 1941.
- MAGATH, T. B. The present status of hydatid (echinococcus) disease in North America. Arch. Int. de la Hidatid., 11: 193, 1950.
- POORE, T. N., MARVIN, C. P. and WALTERS, W. Echinococcal cysts obstructing the common bile duct-report of a case. Arch. Surg., 59: 1001, 1949.
- Scott, I. H. and Scott, G. D. Echinococcus cysts of the liver. Two proven case reports and one suspected case report. J. Indiana State M. A., 42: 454, 1949.
- HOLLIFIELD, W. C. and WILSON, R. Echinococcus infection, report of a case in an immigrant in South Carolina. J. South Carolina M. A., 45: 359, 1949.
- Perkins, C. W. Large hydatid cyst of the liver. Case report. Am. J. Roentgenol., 64: 473, 1950.
- Bell, L. G., Yon, J. L. and Williams, D. J., Jr. Echinococcus cysts of the liver with a report of two cases. U. S. Armed Forces M. J., 2: 1851, 1951.
- Tucker, H. A. Hydatid disease at the Los Angeles County Hospital 1936-1948 with a report of the first autochthonous case from California. Am. J. Trop. Med., 31: 83, 1951.
- Trop. Med., 31: 83, 1951.
 20. Carlquist, J. H. and Dowell, R. J. Echinococcus disease. Rocky Mt. M. J., 48: 773, 1951.
- 21. Bancroft, F. W. Giant echinococcus cyst of the spleen. Rev. Gastroenterol., 18: 882, 1951.
- ATLAS, D. H. and KAMENAR, H. Rupture of echinococcus cysts into the bile ducts simulating stones in the common duct. Am. J. Med., 13: 384, 1952.

- 23. Sedgwick, C. E. Hydatid cysts of the liver. S. Clin. North America, 32: 899, 1952.
- 24. JOHNSTON, J. H. and TWENTE, G. E. Pulmonary hydatid (echinococcus) cyst; report of a native case. Ann. Surg., 136: 305, 1952.
- 25. BAURYS, W. Echinococcus disease of the kidney. J. Urol., 68: 441, 1952.
- 26. RENNER, R. R., ROEMER, F. and TELLE, L. O. Resection of left lobe of liver for echinococcus cyst. Arch. Surg., 66: 257, 1953.
- 27. WILLIAMS, C. Echinococcus disease. South. M. J., 46: 1104, 1953.
- 28. HAYES, J. H. Massive echinococcus cyst of the liver. Am. J. Surg., 87: 297, 1954.
- 29. KELLSEY, D. C. and SPRAT, H. F. Echinococcus disease of bone, report of a case. J. Bone & Joint Surg., 36: 1241, 1954.
- 30. BERGER, I. R. and COWART, G. T. Renal echinococcus disease. Radiology, 62: 852, 1954.
- 31. Lewis, J. E. and Hurwitz, A. Pulmonary echinococcus cyst. Report of a case. Arch. Surg., 69: 746, 1954.
- 32. ZELLMAN, S. L. Echinococcus disease in an American veteran. U. S. Armed Forces M. J., 6: 1800,
- 33. NEGRI, M. and STIRRETT, R. I. Pulmonary hydatid disease: report of a case. California Med., 82: 125,
- 34. ASCHNER, P. W. and GECHMAN, E. Echinococcus renal cyst cured by partial nephrectomy. J. Urol., 76: 23, 1956.
- 35. FEATHER, H. E., KUHN, C. C., RIKE, P. M. and Bass, M. A. Hydatid cyst of the liver. Am. J. Surg., 91: 452, 1956.
- F. Les localizations de l'echinococcose 36. Dévé, primitive chez l'homme. Nécessité d'une revision des statistiques. Compt. rend. Soc. de biol., 74: 735, 1913.
- 37. ARCE, J. Hydatid disease (hydatidosis). Arch. Surg., 42: 1, 1941.
- 38. ELLIS, C. Echinococci in the human liver. Boston M. & S. J., 54: 344, 1856.
- 39. Ellis, C. On a case of echinococcus cyst. Boston M. & S. J., 90: 553, 1876.
- 40. VICKERY, H. F. Primary echinococcus cysts of the pleura. Tr. A. Am. Physicians, 15: 379, 1900.
- 41. Davis, L. and Balboni, G. M. A study of twentynine cases of echinococcus disease at the Massachusetts General Hospital. Boston M. & S. J., 176: 726, 1917
- 42. Balboni, G. M. Hydatid cyst of the lung, report of two cases. Boston M. & S. J., 187: 879, 1922.
- 43. Case records of the Massachusetts General Hospital #12173. Boston M. & S. J., 194: 798, 1926.
- 44. Case records of the Massachusetts General Hospital #18242. New England J. Med., 206: 1270, 1932.
- 45. Case records of the Massachusetts General Hospital #25031. New England J. Med., 220: 113, 1938.
- 46. Case records of the Massachusetts General Hospital #28132. New England J. Med., 226: 538, 1942.
- 47. Case records of the Massachusetts General Hospital #34312. New England J. Med., 239: 205, 1948.
- 48. Case records of the Massachusetts General Hospital #38091. New England J. Med., 246: 341, 1952.
- 49. Massachusetts General Hospital: case records from the medical grand rounds. Am. Pract., 7: 476, 1956.

- 50. Case records of the Massachusetts General Hospital #38211. New England J. Med., 246: 827, 1952
- 51. Case records of the Massachusetts General Hospital #41462. New England J. Med., 253: 878, 1955.
- 52. Case records of the Massachusetts General Hospital #42522. New England J. Med., 255: 1247, 1956.
- 53. Case records of the Massachusetts General Hospital #43322. New England J. Med., 257: 285, 1957
- 54. RAUSCH, R. Studies on the helminth fauna of Alaska. xx. The histogenesis of the alveolar larva of echinococcus species. J. Infect. Dis., 94: 178, 1954.
- 55. RAUSCH, R. and SCHILLER, E. L. Studies on the helminth fauna of Alaska. xxiv. Echinococcus sibiricensis N. sp., from St. Lawrence Island. J. Parasit., 40: 660, 1954.
- 56. RAUSCH, R. and SCHILLER, E. L. Studies on the helminth fauna of Alaska. xxv. The ecology and public health significance of Echinococcus sibiricensis (Rausch and Schiller, 1954) on St. Lawrence Island. Parasitology, 45: 395, 1956.
- 57. RAUSCH, R. Studies on the helminth fauna of Alaska. xxx. The occurrence of Echinococcus multilocularis (Leuckart, 1863) on the mainland of Alaska. Am. J. Trop. Med., 5: 1086, 1956.
- 58. DEW, H. R. The histogenesis of the hydatid parasite (Taenia echinococcus) in the pig. M. J. Australia, p. 101, 1925.
- 59. DEW, H. R. The mechanism of daughter cyst formation in hydatid disease. M. J. Australia, p. 451, 1926.
- 60. RILEY, W. A. Maintenance of echinococcus in the United States. J. Am. Vet. A., 95: 170, 1939.
- 61. MILLER, M. J. Hydatid infection in Canada. Canad. M. A. J., 68: 423, 1953.
- 62. CARMALT-JONES, D. W. Hydatid disease as a clinical problem, some New Zealand experiences. Brit. M. J., p. 5, 1929.
- 63. Godfrey, M. F. Hydatid disease. Clinical, laboratory and roentgenographic observations. Arch. Int. Med., 60: 783, 1937.
- 64. WILSON, W. W. Hepatic hydatid disease. Brit. J. Surg., 37: 453, 1950.
- 65. KELLAWAY, C. H. and FAIRLEY, K. D. The clinical significance of laboratory tests in the diagnosis of hydatid disease. M. J. Australia, p. 340, 1932.
- 66. REAY, E. R. and ROLLESTON, G. L. Diagnosis of hydatid cyst of the kidney. J. Urol., 64: 26, 1950.
- 67. Davidson, L. R. Hydatid cysts of the lung. J. Thoracic Surg., 13: 471, 1944.
- 68. ARCE, J. Hydatid disease (hydatidosis). Hydatid
- cyst of the lung. Arch. Surg., 43: 789, 1941.
 69. Fairley, K. D., Fairley, N. M. and Williams, F. E. Some fallacies in the intradermal test for hydatid disease. M. J. Australia, p. 3, 1929.
- 70. Rose, H. M. and Culbertson, J. T. The diagnosis of echinococcus (hydatid) disease by immunologic reactions with substitute taenia antigens. J. A. M. A., 115: 594, 1940.
- 71. CULBERTSON, J. T. and ROSE, H. M. Further observations on skin reactions to antigens from heterologous cestodes in echinococcus disease. J. Clin. Invest., 20: 249, 1941.
- 72. Dew, H. R., Kellaway, C. H. and Williams, F. E. The intradermal reaction in hydatid disease and its clinical value. M. J. Australia, p. 471, 1925.

- 73. Fairley, K. D. The intradermal test in hydatid disease: a critical analysis of its results. M. J. Australia, p. 472, 1929.
- MAGATH, T. B. Diagnostic tests for hydatid disease based on immunologic phenomena. Arch. Int. de la Hidatid., 13: 218, 1953.
- 75. FAIRLEY, K. D. and WILLIAMS, F. E. The complement fixation test in hydatid disease: an analysis of its results. *J. Coll. Surg. Australia*, p. 1, 1930.
- JORGE, J. M. and RE, P. M. Tratamiento biologico de la hidatidosis. Arch. Int. de la Hidatid., 13: 229, 1953.
- 77. FAIGUENBAUM, J. and FANTA, E. Tratamiento biologico de la hidatidosis. Arch. Int. de la Hidatid., 13: 213, 1953.
- 78. Dew, H. R. Primary cerebral hydatid disease. Australian & New Zealand J. Surg., 24: 161, 1955.
- 79. WADDLE, N. Pulmonary hydatid disease. A review of 478 cases reported in the Louis Barnett Hydatid Registry of the Royal Australasian College of Surgeons. Australian & New Zealand J. Surg., 19: 273, 1950.
- 80. Barrett, N. R. and Thomas, D. Pulmonary hydatid disease. Brit. J. Surg., 40: 222, 1952.
- 81. Dew, H. R. Operative treatment of hydatid cysts of the liver. Surg., Gynec. & Obst., 48: 239, 1929.
- 82. Arce, J. Hydatid cyst of the liver. Arch. Surg., 42: 973, 1941.
- 83. BOURGEON, R. H., PIETRI, H., PANTIN, J. P.,

- CATALANO, H. and GUNTZ, M. Hépatectomie réglée pour kyste hydatique du foie (6 observations). Mém. Acad. de chir., 79: 708, 1953.
- 84. Neuman, Z. Surgical treatment of hydatid cyst of the liver. *Postgrad. Med.*, 14: 304, 1953.
- 85. Saint, C. F. M. Hydatid disease: some features, familiar and not so familiar. Clin. Proc., 7: 315, 1948
- 86. JIDEJIAN, Y. Hydatid disease. Surgery, 34: 155, 1953.
- 87. Schwartz, B. Discussion of Dr. John B. Poole's paper. Am. J. Trop. Med., 6: 430, 1957.
- 88. Magath, T. B. The importance of sylvatic hydatid disease. J. Am. Vet. A., 125: 411, 1954.
- 89. Holzworth, J. Personal communication.
- SWEATMAN, G. K. Distribution and incidence of Echinococcus granulosus in man and other animals with special reference to Canada. Canad. J. Pub. Health, 43: 480, 1952.
- 91. RAUSCH, R. and SCHILLER, E. L. Hydatid disease (echinococcosis) in Alaska and the importance of rodent intermediate hosts. *Science*, 113: 57, 1951.
- Meltzer, H., Kovacs, L., Orfort, T. and Matos, M. Echinococcus in North American Indians and Eskimos. Canad. M. A. J., 75: 121, 1956.
- POOLE, J. B. Echinococcus disease in Northern North America. Am. J. Trop. Med., 6: 424, 1957.
- Wolfgang, R. W. and Poole, J. B. Distribution of echinococcus disease in Northern Canada. Am. J. Trop. Med., 5: 869, 1956.

Phosphate Diabetes*

A Case Study of Osteomalacia

BOY FRAME, M.D. and RICHMOND W. SMITH, JR., M.D. Detroit, Michigan

STEOMALACIA is rarely encountered in this country and when seen it is usually secondary to intestinal malabsorption. The disease as a result of excessive calcium and phosphorus loss, occurring in certain disorders of the renal tubules, is even less frequent. This report concerns a patient with treatment-resistant osteomalacia of such severity that both pseudoand pathological fractures were the disabling consequences. When conventional therapeutic measures appeared inadequate, additional studies were carried out to define the metabolic defect. The initial designation of vitamin D-resistance was later replaced by the more descriptive and generally more acceptable term, phosphate diabetes with resulting osteomalacia. The observations and treatment, extending over a seven-year period, ultimately resulted in notable clinical improvement, the major portion of which followed the addition of supplementary phosphorus to the diet.

CASE REPORT

A thirty-five year old mother of two was first admitted to the Henry Ford Hospital (No. 609372) in 1950 with the complaint of back and leg pain. She had been born at full term by spontaneous delivery and had no history of rickets or other bone deformity. Pregnancies at ages twenty-six and twenty-eight years were normal and terminated in the birth of healthy infants. Calcium supplements were taken during both pregnancies, and she chose to nurse only the first child. The family history was free of bone disease.

Pain in the feet and low back, first experienced at age thirty, was initially considered by several physicians as being of psychoneurotic origin. Over an eight-year period she gradually lost 5 inches in height and several non-healing fractures of the arms, legs and pelvis developed following relative minor trauma. When first seen at the Henry Ford Hospital

in 1950 the pertinent findings were obesity, marked generalized weakness and intense bone tenderness. The serum calcium was 11 mg. per cent; inorganic phosphorus, 2 mg. per cent; and alkaline phosphatase, 3.9 to 6.6 Bodansky units. The urinary calcium excretion averaged 60 mg. per twenty-four hours while the patient was receiving a daily calcium intake of 200 mg. Extensive abnormalities were found in the skeletal x-rays. Comminuted fractures were present in the pubic rami and numerous pseudofractures were noted in the left humerus, right ulna (Fig. 1A) and in several of the metacarpal and metatarsal bones. Demineralization and coarsened trabeculation of bone were also present. The hemoglobin was 13.1 gm. per cent; the leukocyte count 6,600 per cu. mm. with a normal differential, the Wassermann test was negative, and the prothrombin time was 90 per cent.

From April, 1951 to March, 1956, she received approximately 100,000 units of vitamin D and 3.6 gm. of calcium lactate daily. On this program her profound weakness improved slightly but continued bone pain necessitated confinement to a wheel chair. In 1955 she was given a four month trial of methyltestosterone, 10 mg. daily, without clinical improvement. In March, 1956, minimal calcium deposition at the fracture sites was noted in the progress x-rays (Fig. 1B). The levels of serum calcium, phosphorus and alkaline phosphatase were unchanged. For the following three months she received 180,000 units of vitamin D daily and in June, 1956, was admitted for further study. The urine specific gravity was 1.026; pH, 4.5; sugar and albumin negative, and sediment normal. The urea clearance was 73 cc. per minute and phenolsulfonphthalein excretion, 66 per cent in two hours. The oral glucose tolerance test was normal. Five fasting serum inorganic phosphorus values averaged 2.1 and, following the oral administration of phosphorus supplements, seven values averaged 2.8 mg. per cent. The serum calcium ranged between 9.4 and 10.5 mg. per cent; during phosphate supplements the values were from 9.8 to 10.6 mg. per cent. The serum alkaline phosphatase was 5.2 Bodansky units. The serum bicarbonate was 24.5; serum chloride,

^{*}From the Divisions of General Medicine and Endocrinology, Henry Ford Hospital, Detroit, Michigan.

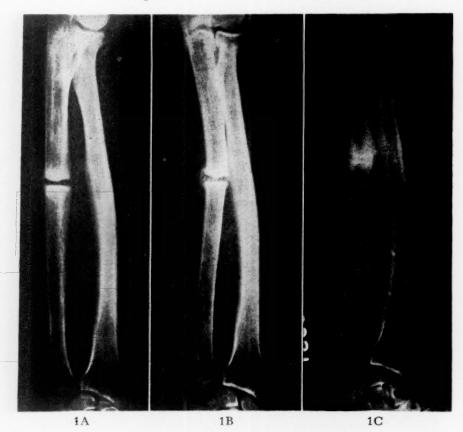


Fig. 1. A, radiograph in 1951 of right ulna fracture before treatment. Note minimal calcification of callus and coarsened trabeculae. B, radiograph in 1956 after five years of vitamin D and calcium therapy. Note further calcification at fracture site and lessened trabeculation. C, radiograph in 1957 after the addition of oral phosphorus supplements, showing complete healing of previous fracture.

100; serum sodium, 133; and serum potassium, 2.8 mEq./L. (average values). The serum albumin was 5.0 and serum globulin 2.2 gm. per cent. Tubular reabsorption of phosphorus was 84 per cent. (Table I.) Urinary 17-ketosteroids were 4.8 and 17-hydroxysteroids 16.1 mg. per twenty-four hours. X-ray films of the small bowel were normal.

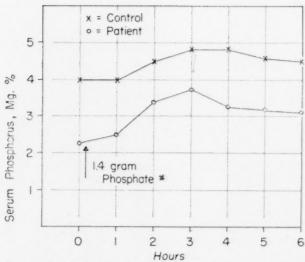
The daily diet at this time contained 9.04 gm. of nitrogen, 408 mg. of calcium and 768 mg. of phos-

phorus. Calcium lactate, 3.6 gm. daily, increased the daily calcium intake to a total of 846 mg. The daily calcium storage during the initial balance periods averaged 242 mg., while phosphorus balance was slightly negative. The average nitrogen balance was negative to the extent of 1.14 gm. per day. During the next four balance periods the patient received additional phosphorus orally, approximately 3 gm. daily, in the form of a mixed sodium phosphate

TABLE I
TUBULAR REABSORPTION OF PHOSPHORUS

			Urine		Ser	Per Cent	
Date of Test	Vol. (ml.)	Time (hr.)	A.	Creatinine (mg./vol.)	Phosphorus (mg. %)	Creatinine (mg. %)	Reabsorption*
June, 1956	435 650	3.0	97.2 23.9	141 211	2.2	0.5 0.5	84 80

^{*} TRP = $1 - \frac{\text{urine phosphorus} \times \text{serum creatinine}}{\text{serum phosphorus} \times \text{urine creatinine}}$



* 100 ml of Na₂ HPO₄ and Na H₂ PO₄ Solution (see previous footnote)

Fig. 2. Demonstration of comparable rise in serum inorganic phosphorus in patient and control subject following oral ingestion of phosphorus.

solution.* Daily calcium retention now averaged 388 mg. and phosphorus retention during the last two balance periods averaged 399 mg. (Table II.)

For the next eight months she continued at home on these vitamin D, calcium lactate and phosphorus supplements, except that mild diarrhea forced a reduction of the phosphate solution intake to 2 gm. daily. Definite symptomatic improvement was apparent in her renewed strength and marked decrease in bone tenderness. Accordingly, she was able with crutches to leave the wheel chair four to five hours daily. This improvement has continued.

In February, 1957, she was again admitted for further metabolic studies. The twenty-four hour urine was negative for sugar. Liver flocculation tests were negative. The fecal fat was 21 per cent of dry weight while Sudan III stain of stool showed only an occasional fat droplet. Fasting serum vitamin A was 22 mµ. per cent and five hours after the oral administration of 200,000 units of vitamin A, 269 mµ. per cent. The electrophoretic pattern of the serum proteins was normal.

Intravenous pyelograms were normal. In the chromatographic study of urinary amino acids a "super-glycine spot" was found.† The total alpha amino acid nitrogen of a twenty-four-hour urine sample was 159 mg. (normal between 100 and 150 mg.).‡

* This experimental preparation contained disodium hydrogen phosphate anhydrous, (Na₂HPO₄) 196 gm., and sodium dihydrogen phosphate monohydrate, (Na H₂PO₄·H₂O) 47.4 gm., in 4 L. aqueous solution.

† Analysis performed by Dr. C. E. Dent of London, England.

‡ Determinations made by Dr. Paul Bartlett, Edsel B. Ford Institute of Medical Research.

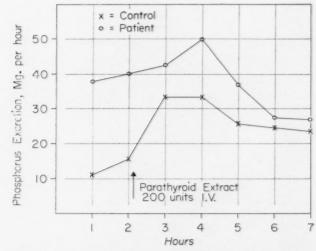


Fig. 3. Changes in urinary phosphorus following intravenous administration of parathyroid extract (Ellsworth-Howard test). The smaller increase for the patient is partly attributed to the initial high rate of phosphorus excretion, but may also be interpreted as indicating an altered renal tubule response to parathyroid extract.

The total serum lipids were 411; serum cholesterol, 139 (66 per cent esters); serum phospholipid phosphorus, 24.9; and serum acid-soluble phosphorus, 5.5 mg. per cent. Five fasting serum inorganic phosphorus values averaged 2.4 mg. per cent. No delay in phosphorus absorption was noted after an oral phosphorus loading test (Fig. 2), while in the Ellsworth-Howard test (Fig. 3) there was only a minimal increase in phosphorus excretion after the intravenous administration of 200 units of parathyroid extract. Tubular reabsorption of phosphorus was now 80 per cent. (Table 1.) Sections of biopsied bone from iliac crest were interpreted by Drs. W. C. Thomas, Jr., and J. E. Howard of Johns Hopkins Hospital to show moderate osteomalacia and normal amounts of alkaline phosphatase in the osteoblasts. Dr. Sissons of University College Hospital, London, England, studying biopsy material obtained at the same time, confirmed the presence of osteomalacia. (Fig. 4.) The daily calcium retention was found to average 443 mg., while phosphorus retention averaged 477 mg. (Table II.) Further healing of the previous pseudofractures was noted in the x-rays. (Fig. 1C.)

In an attempt to elevate the still depressed serum inorganic phosphorus of 2.4 mg. per cent, two of three identified parathyroids were removed. The largest of the resected parathyroids was of normal dimensions, measuring 8 by 4 by 4 mm., and on microscopic study was found to contain an area of chief cell hyperplasia. (Fig. 5.) The second parathyroid, 5 mm. in diameter, was normal on histologic examination. A later needle biopsy specimen of the kidney revealed normal histologic structure and adequate alkaline phosphatase content of the tubules. (Fig. 6.)

After an uneventful recovery the patient was dis-

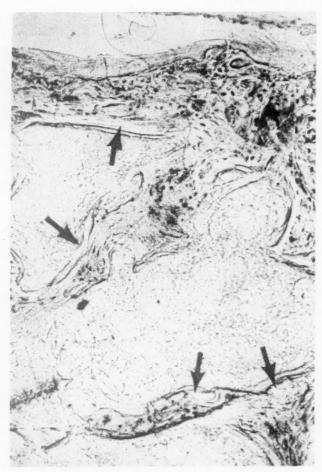


Fig. 4. Photomicrograph of uncalcified bone from iliac crest. Arrows designate areas of osteoid tissue indicating osteomalacia. (Courtesy of Dr. H. A. Sissons, London, England.)

charged, receiving vitamin D and calcium lactate as before. The phosphate supplements were withheld for nearly three months to permit an evaluation of the serum levels of inorganic phosphorus and phospholipids, the latter having been found to be elevated. Four serum inorganic phosphorus values during this period averaged 3 mg. per cent. Two serum phospholipid phosphorus values continued elevated at 17.2 and 21.2 mg. per cent. The serum calcium was 10 mg. per cent on two occasions and alkaline phosphatase 5 Bodansky units. The phosphorus supplements were restored and a subsequent serum inorganic phosphorus value three months later had fallen to 2.4 mg. per cent. Improvement has reached a state where the patient is now both free of pain and ambulatory with crutches.

COMMENTS

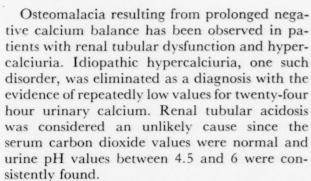
The diagnosis of osteomalacia was made initially from the finding of extensive pseudofractures in a markedly demineralized skeleton. Seven years after the initial clinical diagnosis, a bone biopsy was interpreted to show moderate osteomalacia, even though intensive therapy with vitamin D, calcium lactate and phosphorus administered orally had resulted in improvement demonstrable in roentgenograms. Support for the diagnosis was found in the depressed serum inorganic phosphorus and to a lesser extent in the persistently low urinary calcium. The normal level of serum calcium was not inconsistent with the diagnosis. With the exception of several slightly elevated values, the serum alkaline phosphatase was normal on repeated determinations. While the serum alkaline phosphatase is usually found elevated in osteomalacia [1], normal values have been observed in adults [2,3].

Only minimal improvement followed five years of therapy with 100,000 units of calciferol daily and calcium supplements. During this period there was little contact with the patient and it is possible that had the dosage of vitamin D been significantly increased, further remineralization might have resulted. When studies were resumed in 1956, considerations were given to pathogeneses additional to the originally held but somewhat oversimplified one of "vitamin D-resistant osteomalacia." Steatorrhea, the most commonly encountered disorder which may lead to osteomalacia in adults, was excluded by the normal values for fecal fat, vitamin A absorption and glucose tolerance tests, as well as by the normal x-rays of the small intestinal tract.

Recently, several investigators have called attention to the unusual metabolic disorder of hypophosphatasia, an excellent review of which appeared in 1957 [4]. This disorder, occurring primarily in children, is characterized by bone abnormalities which by x-ray and histologic study are similar to osteomalacia. One differentiating feature is the low concentration of alkaline phosphatase in serum and in tissue where normally it is present. Hypophosphatasia was excluded in our case because of normal to slightly elevated values for serum alkaline phosphatase and normal concentrations of alkaline phosphatase demonstrated in the specific enzyme stains of bone and kidney biopsy specimens. Another distinguishing feature of patients with this condition is the increased amount of urinary phosphoethanolamine, a likely substrate of alkaline phosphatase. In the patient under discussion, no such substance was found by Dr. C. E. Dent who kindly performed the chromatographic studies.



Fig. 5. Hematoxylin-eosin stain of parathyroid section showing chief cell hyperplasia (lower portion) adjacent to oxyphil hyperplasia (upper left).



Other causes of osteomalacia having been excluded, vitamin D resistance as the basic defect was again considered. Since the actions of vitamin D are not completely known, especially as to its effect on bone and kidney, the term "resistance" does not signify a metabolic mechanism. Many support the opinion that vitamin D is not the critical factor in patients diagnosed as having vitamin D-resistant osteomalacia and the term "phosphate diabetes," originally proposed by Fanconi, is now becoming the preferred designation [5]. This implies a

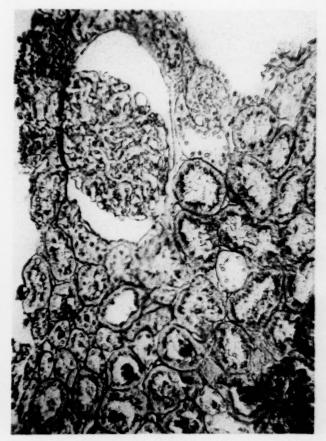


Fig. 6. Phosphatase stain of kidney biopsy material. Darkly stained areas in tubules indicate presence of alkaline phosphatase.

hyperphosphaturia, the limits of which are difficult to define due to the many factors controlling phosphorus excretion. Dent maintains that the disorder is due to a congenital or acquired defect of the renal tubules with hyperphosphaturia and general phosphorus depletion which may be overcome by administering large amounts of vitamin D [6]. Albright considered the hypophosphatemia the result of secondary hyperparathyroidism [7]. In the present case, this latter explanation is not readily acceptable since there was no known initial stimulus such as low serum calcium or high serum phosphorus. In a patient with hypophosphatemia, there is no decisive way of determining by clinical tests which of these two explanations applies. It is possible that a congenital or acquired tubular defect of phosphorus transport can be mediated through an increased responsiveness of the kidney to parathyroid hormone. Tubular reabsorption of phosphorus, measured by the currently popular reabsorption test [8,9], will be found reduced in each situation.

Table II
METABOLIC BALANCE DATA
(Gm. per day)

	Calcium				Phosphorus			Nitrogen					
Date	Six Day Periods	In-	Ou	tput	Balance	In-	Ou	tput	Balance	In-	Out	tput	Balance
		take	Urine	Feces	Dalance	take	Urine	Feces	Datafice	take	Urine	Feces	Datance
June, 1956	I II III * IV * V *	.846 .846 .846 .846 .846	.278 .242 .138 .123 .095 .138	.340 .348 .297 .290 .440 .310	+ .228 + .256 + .411 + .433 + .311 + .398	0.734 † † 3.682		0.166 0.352 0.452 1.013	+.004 044 +.486 +.303	9.04 9.04 9.04 9.04 9.04 9.04	9.55 9.67 9.51 10.36 8.22 8.86	0.51 0.63 0.75 0.63 1.10 0.94	-1.02 -1.26 -1.22 -1.95 -0.28 -0.76
Feb., 1957	ı‡ ı‡	.914	.084	.477	+.353 +.493				+.297 ·+.656	8.25 8.25			

* Supplemental phosphorus solution 75 ml. three times daily; equivalent to 2.948 gm. phosphorus per day. (See case report for composition.)

† Variable intake due to crystals in phosphate solution.

‡ Supplemental phosphorus solution 50 ml. three times daily; equivalent to 1.962 gm. phosphorus per day.

In the present study the phosphorus reabsorption rate was 84 per cent during a period of normal phosphorus intake and 80 per cent eight months later when the phosphorus intake was 2.7 gm. daily. (Table II.) These reabsorption rates are below the lowest value we have observed in normal subjects (86 per cent), and they are less than others have obtained when the urine collection period has been limited to three or four hours [9]. This is evidence of hyperphosphaturia, but in both instances the patient was receiving 180,000 units of vitamin D daily. With conflicting opinions as to its action [7,10] on tubular function, we are unable to say to what extent, if any, the reabsorption tests were affected.

Further evidence of a possible renal tubular defect in patients with phosphate diabetes has been demonstrated in the failure of parathyroid extract to promote a phosphorus diuresis [11], a refractoriness similar to that observed in patients with pseudohypoparathyroidism. An increase of only 20 per cent in phosphorus excretion followed the administration of 200 units of parathyroid extract given intravenously to our patient, while a 300 per cent increase was observed in the normal subject. (Fig. 3.) However, a basal rate of phosphorus excretion in the latter was only one-third to one-fourth that of the patient.

It is possible that tubular rejection of phosphorus already was near maximal in the patient, due either to an intrinsic tubular defect, to the action of vitamin D or to secondary hyperparathyroidism. Perhaps several of these factors were in effect. Accordingly, as with the phosphorus reabsorption test, the demonstration of an abnormal response to parathyroid extract did not define the basic mechanism of the disturbed phosphorus metabolism.

Hyperglycinuria, as evidence of a primary renal disorder in patients with phosphate diabetes, has been reported by Dent and Harris [12]. Urine from our patient was found by Dent to have the "super-glycine spot" on the paper chromatogram of urinary amino acids. Although this is possible additional evidence of a renal tubular defect, glycine is a major amino acid of normal urine, and minor variations in the glycine spot of paper chromatograms may be somewhat difficult to interpret. The total alpha amino acid nitrogen excretion of 159 mg. per twenty-four hours, a slightly elevated value, lends little support to the chromatographic evidence. Other tubular functions, such as concentrating ability, urinary acidification, glucose reabsorption and phenolsulfonphthalein excretion were well preserved. Punch biopsy of the kidney was carried out to determine whether or not there

was histologic evidence of a tubular abnormality. The microscopic appearance was normal and the alkaline phosphatase concentration was considered adequate by histochemical study. (Fig. 6.) In the Fanconi syndrome, a disorder of multiple tubular dysfunctions leading to osteomalacia, a significant reduction of alkaline phosphatase concentration has been demonstrated in the proximal convoluted tubules [13]. A similar finding has been reported in patients with vitamin D-resistant osteomalacia [14].

Although an acquired renal defect seems adequate to explain the hyperphosphaturia and osteomalacia in the present case, other explanations were considered. Failure of phosphate absorption from the intestinal tract was excluded by a prompt rise in serum inorganic phosphorus levels following oral phosphate loading. This increase at least equalled that observed in the normal subject. (Fig. 2.) Urinary phosphorus increased fourfold during the period of high phosphorus supplements, again demonstrating no interference in absorptive rates, while the average levels of fasting serum phosphorus increased only 0.7 mg. per cent.

Brief consideration was given to the possibility of an abnormally avid pool of extraskeletal phosphorus which may have accounted for the lowered serum inorganic phosphorus concentration. The acid-soluble phosphorus fraction of the serum was normal. Quite unexpectedly, however, the concentration of phospholipid phosphorus was significantly increased. The initial value of 24.9 mg. per cent, more than twice the normal concentration, was obtained while the patient was receiving large amounts of phosphorus, supplemental to the vitamin D. When the oral phosphorus was withheld for three months, the phospholipid phosphorus level continued elevated 17.2 and 21.2 mg. per cent, an unaccountable abnormality. Any shunting of phosphorus to the phospholipids would soon saturate this fraction or any other extraskeletal deposit of inorganic phosphorus, such as liver and muscle. This explanation of the hypophosphatemia is untenable and ultimately a net corporal deficit of phosphorus must be held accountable.

Hypophosphatemia in phosphate diabetes, whatever the reason for its persistence, seems essential to the development of the osteomalacia. In the present patient and in those in the literature, the low level of serum inorganic phosphorus has been a conspicuous finding. Hypophos-

phatemia has continued even after prolonged therapy with vitamin D and calcium, and it has been reported after such therapy resulted in reossification [15–17]. The fasting levels of serum phosphorus, determined repeatedly during the June, 1956, hospitalization, were raised an average of 0.7 mg. per cent by the large doses of oral phosphate supplements. Diarrhea forced a reduction of 25 per cent in the phosphate feedings, and in subsequent studies the serum phosphorus values averaged 2.4 mg. per cent, close to the initial low levels. Since considerable remineralization occurred despite continuing hypophosphatemia, additional factors may have been important in the development of the osteomalacia. The concept of a deficient enzyme or cellular function relating to ossification, similar to the condition of hypophosphatasia and suggested by Segar and associates [18] in a similar case of treatment-resistant osteomalacia, is likewise speculative in the present case. The large doses of vitamin D, the calcium and supplemental phosphorus may have forced, by their mass effect, the deficient system to recalcify the depleted osteoid in the presence of a low serum inorganic phosphorus. A preferred explanation is that, although fasting levels of serum inorganic phosphorus were not greatly increased during the period of accelerated improvement, postprandial levels were transiently increased to an extent permitting more rapid ossification.

The first period of therapy covers the five years following initial studies in 1950. During this time the patient remained out of contact with a physician but continued daily the self administration of 3.6 gm. calcium lactate and approximately 100,000 units of vitamin D. After five years of this unsupervised treatment she reported a definite although limited improvement in muscle strength. Remineralization of minimal extent was seen in the skeletal x-ray films (Fig. 1B) but there was no decrease in bone tenderness. Values for serum calcium, phosphorus and alkaline phosphatase remained essentially unchanged. Methyltestosterone, 10 mg. daily, was given on the assumption that osteoporosis due to immobilization or other causes was complicating the osteomalacia. After four months no improvement was noted and the hormone was discontinued because of facial hypertrichosis.

The second phase of therapy was initiated in March, 1956, by an increase in vitamin D dosage

to 180,000 units daily. However, after three months there was no demonstrable change in the clinical or laboratory indices. In the subsequent metabolic studies of this treatment phase the phosphorus balance was found slightly negative while calcium retention was 240 mg. daily. (Table II.) The discrepancy between the calcium and phosphorus balances is related in part to the negative nitrogen balance of this experimental period. The latter is considered the result of almost complete immobilization and the borderline protein intake given to approximate the level of home consumption. When neither further clinical improvement nor significant phosphorus retention followed the aforementioned increase in vitamin D, oral phosphorus supplements were added to the vitamin D and calcium lactate therapy. Phosphorus balance became markedly positive, calcium retention increased (Table 1) and within a few weeks the patient reported greater muscle strength and complete disappearance of bone tenderness. The large dose vitamin D, calcium lactate and phosphorus supplements were continued uninterruptedly for eight months, during which time clinical improvement was maintained. Metabolic balance studies were repeated and favorable storage rates for calcium and phosphorus again confirmed. (Table II.) In contrast to minimal changes noted after the initial five years of therapy, striking remineralization was now apparent after eight months of supplementary phosphorus. Although some improvement probably resulted from the increased dose of vitamin D, both the control of symptoms and results from metabolic balance studies indicated that the accelerated reossification followed the use of phosphorus supplements. Vitamin D alone when used in doses approximating 1,000,000 units daily has been effective in similar cases, but vitamin toxicity has been a limiting factor in some patients. The present combination of modest amounts of vitamin D supplemented with intensive phosphate feeding prevented this complication.

Dent [2] remains undecided as to the value of additional dietary phosphorus for patients with phosphate diabetes. Saville and Nassim [20], however, report that the addition of sodium phosphate salts to the diet of such a patient furthered the retention of calcium and phosphorus. Darrow, quoted by Petersen [21], studied a patient with vitamin D-resistant osteomalacia and low serum phosphorus (phos-

phate diabetes) in whom added oral phosphorus gave symptomatic relief.

As mentioned previously, the osteomalacia of phosphate diabetes can be corrected in spite of continuing hypophosphatemia. It is reasonable that the healing process might be further accelerated by elevating the serum inorganic phosphorus. Howard [22] has considered parathyroidectomy as a means to accomplish this. Henneman [19] had 85 per cent of hyperplastic parathyroid tissue removed from a similar patient with osteomalacia after which procedure calcium and phosphorus retention increased. Accordingly, the third phase of treatment in the present case began when two of the three visualized parathyroids were removed. The serum inorganic phosphorus levels increased immediately and in the subsequent five months have averaged 0.6 mg. per cent higher than the immediate preoperative values. The trend in serum phosphorus levels, however, has been gradually down to preoperative values. No changes have been noted in the levels of serum calcium and alkaline phosphatase, while the previously initiated clinical improvement has continued. To what extent, if any, parathyroidectomy has helped, unfortunately, cannot be established since subsequent metabolic balance studies were not carried out. It is a major surgical procedure and not to be considered until the more conservative measures have failed.

SUMMARY

A case report is presented of a patient with vitamin D-resistant osteomalacia. The basic defect was considered to be a reduced renal tubular reabsorption of phosphorus with resulting hypophosphatemia. After lengthy therapy with calcium lactate and large doses of vitamin D was only partially successful, supplemental phosphorus administered orally resulted in marked improvement. Symptoms abated, calcium and phosphorus retention increased, and reossification was noted in x-ray films of the demineralized skeleton. Parathyroidectomy was performed but its contribution to the over-all results cannot be stated.

REFERENCES

- BARTTER, F. C. Osteoporosis. Am. J. Med., 22: 797, 1957.
- 2. Dent, C. E. Personal communication, 1957.
- 3. PEDERSEN, H. E. and McCarroll, H. R. Vitaminresistant rickets. J. Bone & Joint Surg., 33-A: 203, 1051

- 4. Fraser, D. Hypophosphatasia. Am. J. Med., 22: 730, 1957
- Follis, R. H., Jr. A survey of bone disease. Am. J. Med., 22: 469, 1957.
- Dent, C. E. Rickets and osteomalacia from renal tubule defects. J. Bone & Joint Surg., 34-B: 266, 1952.
- Albright, F. and Reifenstein, E. C. The Parathyroid Glands and Metabolic Bone Disease. Baltimore, 1948. Williams & Wilkins Co.
- 8. CHAMBERS, E. L., JR., GORDAN, G. S., GOLDMAN, L. and REIFENSTEIN, E. C. JR. Tests for hyperparathyroidism: tubular reabsorption of phosphate, phosphate deprivation, and calcium infusion. J. Clin. Endocrinol., 16: 1507, 1956.
- SCHAAF, M. and KYLE, L. H. Measurement of per cent renal phosphorus reabsorption in the diagnosis of hyperparathyroidism. Am. J. M. Sc., 228: 262, 1954.
- 10. Harrison, H. E. and Harrison, H. C. The renal excretion of inorganic phosphate in relation to the action of vitamin D and parathyroid hormone. *J. Clin. Invest.*, 20: 47, 1941.
- 11. FANCONI, G. Variations in sensitivity to vitamin D: from vitamin D-resistant rickets, vitamin D avitaminotic rickets, and hypervitaminosis D to idiopathic hypercalcemia. In: Ciba Foundation Symposium on Bone Structure and Metabolism. Boston, 1956. Little, Brown & Co.

- Dent, C. E. and Harris, H. Hereditary forms of rickets and osteomalacia. J. Bone & Joint Surg., 38-B: 204, 1956.
- STOWERS, J. M. and DENT, C. E. Studies on mechanism of Fanconi syndrome. Quart. J. Med., 16: 275, 1947
- SNAPPER, I. and NATHAN, D. J. Rickets and osteomalacia. Am. J. Med., 22: 939, 1957.
- FREEMAN, S. and DUNSKY, I. Resistant rickets. Am. J. Dis. Child., 79: 409, 1950.
- Albright, F., Butler, A. M. and Bloomberg, E. Rickets resistant to vitamin D therapy. Am. J. Dis. Child., 54: 529, 1937.
- STEARNS, G. and BOYD, J. D. The healing of rickets coincident with low serum inorganic phosphorus. J. Clin. Invest., 10: 591, 1931.
- SEGAR, W. E., IBER, F. L. and KYLE, L. H. Osteomalacia of unknown etiology. New England J. Med., 254: 1011, 1956.
- 19. Henneman, P. H. Personal communication, 1957.
- SAVILLE, P. D., NASSIM, J. R., STEVENSON, F. H., MULLIGAN, L. and CAREY, M. The effect of A.T. 10 on calcium and phosphorus metabolism in resistant rickets. Clin. Sc., 14: 489, 1955.
- Peterson, R. E. Hypophosphatemic rickets; description and case reports of renal tubular form of this deficiency disease. J. Kansas M. Soc., 57: 582, 1956.
- 22. Howard, J. E. Personal communication, 1957.

Paradoxical Embolism with Renal Failure Caused by Occlusion of the Renal Arteries*

THOMAS J. GILL, III, M.D. and GUSTAVE J. DAMMIN, M.D.

New York, New York

Boston, Massachusetts

Paradoxical embolism is defined as the passage of an embolus from a source on the venous side of the systemic circulation to the arterial side of the systemic circulation without having traversed the pulmonary circulation. This definition also includes cases in which an embolus is wedged in a septal defect with part on the venous side and part on the arterial side of the systemic circulation without evidence of peripheral arterial emboli.

The pathogenesis of paradoxical embolism was first elucidated by Cohnheim in 1877 [2]. It was further discussed and amplified by Rostan in 1884 [6] and by Zahn in 1889 [12]. There have been several reviews since then, notably those of Ohm (1907) [20], Thompson and Evans (1929) [47], and Young (1948) [67]. In reports on 100 cases of paradoxical embolism [1-67], the kidneys were involved in thirty-five cases (35 per cent). In no case had (1) the renal arteries been the only systemic arteries involved, (2) renal insufficiency occurred, and (3) renal insufficiency been the cause of death. In the case to be described, the veins in one lower extremity were the apparent site of the initial thrombosis, there were large emboli in the lungs, there was a patency of the atrial septum, and the cause of death was embolic occlusion of the renal arteries resulting in extensive infarction and renal insufficiency.

CASE REPORT

This was the first admission to the Peter Bent Brigham Hospital for W. B. (Hosp. No. 9K900, Autopsy No. A-57-210), a fifty-six year old white mother of two who was referred here because of severe oliguria of four days' duration.

Three weeks prior to admission she had fallen and fractured the distal portion of the left fibula. A cast had been applied and she had been put to bed. One week prior to admission a severe frontal headache, nausea and vomiting had developed. The following

day she had noticed vague right flank pain. Two days later the twenty-four-hour urine output had been approximately 20 cc. On the day before admission, 4,000 cc. of fluid had been administered and the urine output had amounted to only 40 cc. Because of continued severe oliguria she was transferred to this hospital.

The patient was markedly obese, weighing 291 pounds on admission. She was alert, oriented, cooperative, and in no apparent distress. Her blood pressure was 220/120 mm. Hg in the right arm and 150/80 mm. Hg in the left arm. There were no abnormalities of the ocular fundi. There was questionable tenderness in the right costovertebral angle and moderate pitting edema of the right ankle. The neurological examination was within normal limits. The rest of the physical examination was not contributory.

On the day following admission the urine output consisted of 280 cc. of grossly blood-tinged urine which had a pH of 7.5 and contained 3-plus protein. At this time, the serum sodium was 122 mEq./L.; potassium, 5.6 mEq./L.; chloride, 87 mEq./L.; carbon dioxide, 18.6 mM./L.; blood urea nitrogen, 90 mg. per cent; and hematocrit, 38 per cent. The

electrocardiogram was normal.

The oliguria persisted until the seventh hospital day when improvement in renal function appeared. The urine output was 635 cc. with specific gravity of 1.010. At this time the serum sodium was 137 mEq./L.; potassium, 6.3 mEq./L.; chloride, 99 mEq./L.; carbon dioxide, 13.4 mM./L.; blood urea nitrogen, 165 mg. per cent; and calcium, 5.2 mEq./L. The urine output ranged from 250 to 1,200 cc. daily for the next sixteen days. During this period her clinical state was fairly satisfactory except for some vomiting. The serum sodium ranged between 121 and 143 mEq./L.; potassium, between 5.3 and 6.6 mEq./L.; chloride, between 82 and 99 mEq./L.; carbon dioxide, between 12.5 and 15.4 mM./L.; and blood urea nitrogen, between 165 and 290 mg. per cent. On the twenty-fourth hospital day however, the urine output fell to 145 cc. and the blood urea nitrogen rose to 345 mg. per cent. That night the patient became very restless and obtunded; she spoke constantly, and had hypoactive knee jerks. Her

^{*} From the Department of Pathology, Peter Bent Brigham Hospital, Boston, Massachusetts.

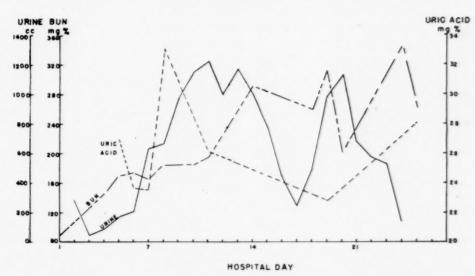


Fig. 1. Variations in urine output, blood urea nitrogen and serum uric acid during the course of the renal failure.

clinical condition deteriorated progressively, the oliguria persisted, and on the twenty-seventh hospital day, the patient died.

During the entire hospital stay, the serum uric acid had been elevated, varying between 23.6 and 33.0 mg. per cent. The variation in serum uric acid level did not correspond to the variation in urine output or blood urea nitrogen. Figure 1 shows the variation in urine output, blood urea nitrogen and serum uric acid during her hospital course.

During the entire hospital stay there had been no significant electrocardiographic changes. She remained hypertensive and essentially afebrile until two days prior to death when the systolic pressure fell to 106 mm. Hg and her temperature rose to 101°F.

Two days before death Staphylococcus aureus was cultured from the venous catheter tip, and it was also cultured from the heart blood at autopsy.

At autopsy, gross examination confirmed the obesity as extreme. The cast on the fractured left fibula had been removed. There was no evidence of infection at the fracture site. A thrombus was found in the deep veins of the left calf. The lung weights were within normal limits, the right weighing 360 gm. and the left, 340 gm. Thromboemboli were found in the primary and secondary branches of the pulmonary artery. There was congestion of the lung bases posteriorly and an area of hemorrhage measuring 6 by 1 by 1 cm. in the lower lobe of the left lung. No thrombi were evident in the pulmonary veins. The heart was enlarged, weighing 430 gm. There was hypertrophy of the ventricles, right ventricular dilatation, and partial replacement of the myocardium of the right ventricle by adipose tissue. The foramen ovale was widely patent and measured 1.8 by 1.4 cm. on the right atrial side and 1.7 by 0.8 cm. on the left atrial side. The valve of the foramen ovale was mobile and contained a saccular dilatation which

bulged 1.2 cm. into the left atrium. A probe 1.0 cm. in diameter was easily passed through the foramen ovale. (Fig. 2.) Both coronary arteries were free from atheroma and patent to their termination at the apex. There were no thrombi in the atria. The right kidney weighed 170 gm. and measured 10.0 by 6.2 by 3.4 cm., the left kidney weighed 235 gm. and measured 12.0 by 5.8 by 3.8 cm. Both kidneys showed "uric acid infarcts," extensive areas of ischemic necrosis, and some areas of hemorrhage; the right kidney was more extensively involved than the left. There was a thrombus 1.1 cm. long occluding the left renal artery and one occluding the entire length of the right renal artery. (Fig. 3.)

The spleen weighed 170 gm. and had no infarcts. The mesenteric arteries and those of the celiac axis were normal, showing no evidence of occlusion or of significant atherosclerosis. There was no other evidence of peripheral embolization. There were no significant findings in the brain. The gallbladder was distended with bile and contained eight mixed stones. There was fatty infiltration of the pancreas.

No congenital vascular malformation or arterial embolus was found to explain the lower blood pressure in the left arm.

Microscopic examination revealed thrombi and several bronchi filled with purulent exudate in some of the smaller pulmonary arteries and arterioles of the left lung. In the hilar area there was an acute abscess in the lung parenchyma. In the periphery of the lower lobe there was an area of bacterial arteritis with necrosis of vessel walls, colonies of bacteria on the pleural surface, and an area of hemorrhage. The right lung was more extensively involved than the left. In addition to foci of congestion, hemorrhage and atelectasis, thrombi were noted in many small arteries and arterioles. No thrombi were noted in the veins. Bacteria could be seen in the alveolar spaces, lining

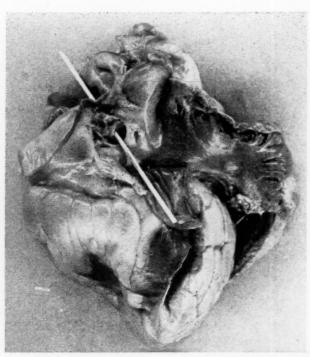


Fig. 2. Widely patent foramen ovale seen from the right atrial aspect of the heart.

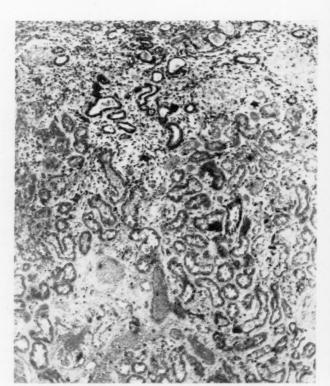


Fig. 4. Ischemic necrosis of the kidney with preservation of the subcapsular cortex in the left upper part of the field. Hematoxylin and eosin stain, 4 micron section.

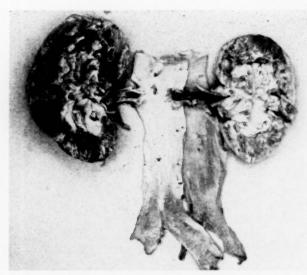


Fig. 3. Thrombi in the renal arteries with massive infarction of both kidneys, more extensive on the right. There is no atherosclerosis of the aorta or of any of its branches, including the renal arteries.



Fig. 5. Renal artery showing site of attachment of the thrombus, calcification in the thrombus, and an intact internal elastic membrane in the artery. Hematoxylin and eosin stain, 4 micron section.

the walls of some of the blood vessels, and in abscesses in the lung parenchyma. The abscesses in the hilar region were of more recent origin than those in the periphery. The myocardium had several recent focal abscesses but otherwise was essentially normal. The mitral valve was normal, there being no evidence of inflammation, vascularization or verruca formation.

In both kidneys there was extensive ischemic necrosis in which the general architectural pattern, but not the cellular detail, of the renal structures was maintained. The outer layer of the cortex showed preservation of the normal renal structure. (Fig. 4.) Many of the tubules were filled with basophilic crystals and some of the glomeruli were enlarged and hemorrhagic. There were foci of calcium in the tubular epithelium and lumen. There was no evidence of gout.

Some of the small arteries and arterioles in the left kidney contained recent thrombi. The thrombus in the main left renal artery was adherent to about 20 per cent of the vessel circumference. (Fig. 5.) The fibrous tissue of the thrombus blended into that of the intima and there was one area of calcification in the thrombus. There was no fragmentation of the elastic tissue. The right kidney showed essentially the same changes as the left kidney but they were more severe and less of the cortex was spared. Some of the small arteries in the papillae contained thrombi, some recent and some partially organized. The thrombus in the right renal artery was adherent to about 40 per cent of the vessel circumference. The fibrous tissue blended into that of the intima, and an area of calcification in the thrombus approximately the same size as that in the left renal artery could be seen. In addition, there was evidence of canalization in the thrombus.

The corpus striatum showed several small recent abscesses consisting of neutrophils and small coccal bacteria. Except for small foci suggestive of old hemorrhage, there were no other significant changes in the brain.

The spleen was congested and without evidence of infarction. The pancreas had moderate fatty infiltration and the liver, slight fatty metamorphosis. The adrenals were normal except for some pseudoacinar formation. The thyroid, parathyroids and pituitary were normal. The aorta had only minimal atheromatous involvement. There were no thrombi in the vena cava or the renal veins.

COMMENTS

Conditions for venous stasis and thrombosis were established when this obese patient required immobilization because of a fracture of the lateral malleolus of the left fibula. She must have had the pulmonary embolization from the fairly recent thrombus in the deep veins of the left calf before the onset of severe oliguria. This would establish the necessary conditions for a rise in the right atrial pressure, thus causing

the flow of blood from right to left. This would carry the emboli to the systemic circulation through the patent foramen ovale. Since she went into renal failure suddenly, both kidneys must have been involved by the emboli either simultaneously or within a short space of time. It is not likely that this would occur with the occlusion of just one renal artery. In addition, the oldest infarcts in each kidney were approximately of the same age. These were probably the only emboli dislodged to the arterial circulation, since no other sites of embolization were found. The right kidney was more severely involved for three reasons. First, the right renal artery thrombus was adherent to the vessel wall by 40 per cent of its circumference while that in the left renal artery was adherent by only 20 per cent of its circumference. The thrombus in the right renal artery was larger than that in the left. Secondly, the right kidney was more extensively infarcted than the left, thus indicating a greater diminution of blood supply. Thirdly, there were both old and recent thrombi in both kidneys, but more old thrombi in the right kidney. This suggests a more complete occlusion of the right renal vessels. The preservation of the normal renal architecture in the subcapsular cortex, especially on the left, was due to the fact that its blood supply comes through small arteries in the capsule which were not occluded by the emboli.

The diuresis had begun on the third hospital day, as would be expected in the usual course of acute renal failure [74,75] and after the seventh hospital day, with one exception (the seventeenth hospital day), the urine output was over 400 cc. daily until two days prior to death. During the entire hospital course, however, the blood urea nitrogen continued to rise. Thus, despite the early onset of the diuretic phase, the patient was not able to maintain the increased urine output and reduce the nitrogen retention. The recent thrombi found in the small intrarenal arteries suggest that during the diuretic phase more infarction had occurred and finally destroyed enough of the remaining functioning parenchyma to prevent resumption of adequate renal function.

The staphylococcus cultured from the venous catheter tip two days before her death was the source of the embolic pneumonitis, the abscesses in the corpus striatum, and the focal abscesses in the myocardium. The pseudoacinar formation in the adrenal is best explained by the septicemia.

The uric acid levels in the serum, which were

Table 1

PARADOXICAL EMBOLISM

Age Incidence in Eighty-seven Cases

Age Range (yr.)	No.	%
0-29	11	13
30-39	12	14
10-49	17	19
50-59	26	30
50-69	12	14
70 and over	9	10

consistently and markedly elevated, did not follow the fluctuations in either urine output or blood urea nitrogen. (Fig. 1.) The presence of "uric acid infarcts" in both kidneys also indicated a persistently elevated serum uric acid.

Including this case, 101 cases of paradoxical embolism, proved at autopsy, have been recorded. Three cases have been reported in which paradoxical embolism was diagnosed clinically and in which the patient recovered [47,49,64]. The criteria used for diagnosis included hemiplegia in two, arterial embolus to the arm in one, phlebitis of the lower extremity in all three, and pulmonary embolism in one; in all three cases the foramen ovale was assumed to be patent. Paradoxical embolism can seldom be established as a clinical diagnosis; for this reason, these cases have not been included in the present analysis of the manifestations of this process. Cases have been reported in which the combination of an infective focus, septic embolic involvement of several organs, especially the brain, and in some an interventricular septal defect were found [68-73]. It is not possible to classify these cases unequivocally as paradoxical embolization because of the strong possibility of the bacteria having traversed the pulmonary circulation to reach the systemic circulation. Thus these cases will not be included in the present analysis of paradoxical embolism.

Paradoxical embolism occurs most frequently in middle aged women, as in the case described here. In eighty-eight cases in which the data were available, fifty-five cases (63 per cent) occurred in women and thirty-three cases (37 per cent) occurred in men. Table I shows the age distribution in the eighty-seven cases in which the data were available. It can be seen that in 49 per cent of the cases the patients fell in the age range of forty to fifty-nine years.

Table II
PARADOXICAL EMBOLISM
Sites of Involvement in 101 Cases

Organ	No. and %
Lung	63
Pulmonary Infarcts	. 11
Brain	36
Kidney	36
Spleen	
Other Arteries	

Table III
PARADOXICAL EMBOLISM
Nature of Sources of Emboli

	Cases	%
Thrombi in Pelvic or Leg Veins	49	58
Thrombus in Right Atrium		15
Tumor Embolism	9	11
Air Embolism	3	4
Other	10	12
	84	100

The major organs involved are the lung, brain, kidney and spleen. Table II shows the frequency of involvement of these organs in all 101 cases studied. In the brain, the arteries most frequently involved were the middle cerebral arteries: right, eight cases (22 per cent) and left, five cases (14 per cent). Both kidneys were involved in nineteen cases (53 per cent); the left alone, nine cases (25 per cent); the right alone, seven cases (19 per cent); and in one case the kidney involved was not specified. In no case of paradoxical embolism involving the kidney was renal insufficiency recorded; in this respect the case reported here is quite unique. In nineteen cases, emboli did not reach the periphery, but the embolus was arrested in the foramen ovale; in sixteen of these cases there were also pulmonary emboli. Of the 101 patients, including both those with and without peripheral emboli, thirty-five (35 per cent) had an embolus wedged in the foramen ovale. This is an example of cardiac embolism.

The etiological factors in the pathogenesis of paradoxical embolism are listed in Table III. The most frequent septal defect is the patent foramen ovale, which occurred in 97 per cent of

these cases. This is not an uncommon finding in the general population. According to Thompson and Evans [47], who studied reports of 1,100 consecutive autopsies, probe-patent (0.2 cm.) foramen ovale occurs in 29 per cent and pencilpatent (0.7 cm.) foramen ovale occurs in 6 per cent of the general population. Considering the frequency of phlebitis in the lower extremities and the relatively high incidence of significantly patent foramen ovale, there is a high potential for the occurrence of paradoxical embolization. In the other 3 per cent of the cases an interventricular septal defect was found.

In the cases in which tumor was found to be the source of the embolus, the thyroid was the most common offender, a carcinoma being the cause in two cases [12] and a sarcoma in two cases [11,16]. There was one case each of sarcoma of the seminal vesicle [12], unspecified tumor of the pancreas [12], teratoma of the testicle [47], carcinoma of the stomach [7] and carcinoma of the cystic duct [65]. The nature of the tumor metastases, the site of the primary tumor, and the sudden onset of symptoms all indicated that a paradoxical embolus had pessed

through the patent foramen ovale.

In order for an embolus to pass through the patent foramen ovale the pressure in the right atrium must exceed that in the left atrium, thus causing the flow of blood from right to left. The experiments of Haggart and Walker on the quantitative occlusion of the pulmonary artery [76] showed that: (1) total occlusion of the left branch of the pulmonary artery increased the pulmonary blood pressure 29 per cent and had no effect on systemic blood pressure; (2) total occlusion of the pulmonary artery increased the pulmonary blood pressure 121 to 267 per cent and decreased the systemic blood pressure, eventually to 0 mm. Hg; and (3) occlusion up to 52 to 64 per cent of the total pulmonary flow caused no change in pulmonary or systemic blood pressure, but just exceeding these levels caused the pulmonary pressure to rise suddenly and the systemic pressure to fall, with death ensuing. Thus, pulmonary artery occlusion of approximately fifty-five per cent would be needed to cause a sufficient rise in right atrial pressure to establish a right to left flow through the patent foramen ovale.

In 38 per cent of the cases no pulmonary emboli were found to explain a rise in pulmonary pressure. There are several possibilities to explain this. First, there may have been a shower

of small emboli that lodged in the small peripheral pulmonary arteries and arterioles, occluded enough of the circulation to cause the requisite increase in right atrial pressure, but escaped detection at autopsy. Secondly, a reflex vasoconstriction of the smaller pulmonary arteries may occur after a shower of small emboli insufficient in themselves to occlude enough of the pulmonary circulation to cause a pressure elevation in the right atrium. Thirdly, a vasoconstrictive humoral substance such as serotonin may be released when the embolus breaks off, and cause a transient pulmonary vasoconstriction sufficient to elevate the pulmonary pressure enough to direct the flow of blood from the right to the left atrium. Serotonin has been shown to increase pulmonary artery pressure and resistance more than the systemic arterial pressure and resistance in pentobarbital anesthetized dogs [77]. Lastly, acute or chronic pulmonary infections or such pulmonary diseases as the pneumoconioses and sarcoid, may cause the requisite rise in right atrial pressure. Pulmonary edema and congestive heart failure cause a rise in left atrial pressure and pulmonary vasospasm with a subsequent rise in right atrial pressure. The latter rise is proportionately greater than that in the left atrium and may thus cause a right to left flow through the patent foramen ovale.

SUMMARY

A case is reported of renal failure due to the passage of emboli from a thrombus in the deep calf veins, through a patent foramen ovale, to occlude both renal arteries in an obese woman following fracture of the fibula.

Paradoxical embolism had been reported and proved at autopsy in 100 previous cases. In 35 per cent of these the kidneys were involved. In no case, however, was the kidney the only organ involved, or did renal insufficiency result, with death from renal failure.

An analysis of all the data available on paradoxical embolism shows that it occurs predominantly in middle-aged women. The lungs, brain, kidneys and spleen are the organs most frequently involved by emboli. A rise in right atrial pressure is necessary to cause the blood to flow from right to left, thus carrying the emboli to the arterial circulation. The possible mechanism causing this rise in cases when there is no evident pulmonary embolization is discussed.

ADDENDUM

Since this paper was submitted for publication six more cases of paradoxical embolism have come to our attention [78–81]. The sources of all the emboli were in the veins of the lower extremities or pelvis. Emboli involved the coronary arteries in three cases, brain in three cases, both kidneys in two cases, peripheral arteries in two cases and the foramen ovale in one case. Three occurred in women aged forty-three, forty-seven, and sixty-nine years and three occurred in men aged thirty-five, sixty-three, and seventy years.

REFERENCES

- COHN, B. Klinik des embolischen Gefässkrankenheit. Berlin, 1860. A. Hirschwald.
- COHNHEIM, J. Vorlesungen über allgemeine Pathologie, vol. 1, p. 144. Berlin, 1877. A. Hirschwald.
- LITTEN, M. Ueber embolische Muskelveränderung und die Resorption toter Muskelfasern. Ein Beitrag zur Frage von der Ueberwanderung embolischen Materials bei offen gebliebenem Foramen ovale. Virchows Arch. f. path. Anat., 80: 281, 1880.
- 4. Louis. Cited by Ballet, G. Arch. gén. de méd., 5: 659, 1880.
- RIEGEL, F. Ueber die Entstehungsbedingungen und die diagnostische Bedeutung des Friedreich'schen diastolischen Venencollapses. Deutsche Arch. f. klin. Med., 34: 245, 1884,
- 6. Rostan, A. Contrib. à l'étude de l'embolie croisée consec. à la persistance du trou de Botal. Thèse, Genève, 1884.
- Poths, H. Beiträge zur Casuistik der Embolie bei offenem Foramen ovale. Inaug. Diss. Giessen, 1887.
- 8. HAUSER, G. Ueber embolische Verschleppung von Thrombenmaterial a. d. rechten Herzen in peripheren. Körperarterien. München. med. Wchnschr., 35: 35, 1888.
- 9. Schmieden, W. Ueber Verschleppung von Thrombenmaterial. Inaug. Diss. Freiburg, 1888.
- SCHMORL, G. Zwei Fälle von Leberruptur mit embolische Verschleppung von Lebergewebe. Deutsch. Arch. f. klin. Med., 42: 499, 1888.
- 11. Bonome, A. Trasporto retrogrado degli emboli nelle vene. *Arch. med.*, 13: 267, 1889.
- ZAHN, W. F. Ueber paradoxe Embolie und ihre Bedeutung für die Geschwulstmetastase. Virchows Arch. f. path. Anat., 115: 71, 1889.
- 13. Lubarsch, O. Zur Lehre von der Parenchymzellenembolie. Fortschr. d. Med., 11: 805, 1893.
- Jaenicke, O. Ueber das Foramen ovale cordis. Dissert. Kiel, 1894.
- 15. MARCHAND, F. Zur Kenntniss der Embolie und Thrombose der Gehirnarterien, zugleich ein Beitrag zur Casuistik der primären Herztumoren und der gekreuzten Embolie. Berl. klin. Wchnschr., p. 1, 1894.
- Scheven, U. Zur Lehre von der atypischen Embolie. Inaug. Diss. Rostock, 1894.

- RABE. Persistance du Conduit du Botall et embolie paradoxales. Gaz. hebdom. de med. et chir., 35: 413.
- Ems, F. Persistanz des Foramen ovale und paradoxe Embolie. Inaug. Diss. München, 1907.
- HOCHEISEN, P. Embolie der Arteria fossae Sylvii durch einen Venenthrombus des Unterschenkels bei Offenstehen des Foramen ovale. Fortschr. d. Med., 22: 393, 1904.
- 20. Онм, J. Klinische Beobachtungen bei offenem Foramen ovale und ihre diagnostische Bedeutung. Ztschr. f. klin. Med., 61: 374, 1907.
- SÄNGER. Cited by Ohm, J. Klinische Beobachtungen bei offenem. Foramen ovale und ihre diagnostische Bedeutung. Ztschr. f. klin. Med., 61: 374, 1907.
- STOERK, O. In Verhandlungen ärztlicher Gesellschaften und Kongressberichte. Wien klin. Wehnschr., 20: 1555, 1907.
- Kyber, K. Ueber zwei Fälle von paradoxer Embolie. Inaug. Diss. Leipzig, 1909.
- 24. Mönckeburg, J. G. Embolus in Foramen ovale Deutsch. med. Wchnschr., 1044, 1909.
- 25. Thilo, L. Zur Kenntnis der Missbildung des
- Herzen. Inaug. Diss. Leipzig, 1909. 26. Versé, M. Ueber paradoxe Embolie. Verhandl.
- Deutsch. path. Gesell., 13: 219, 1909.

 27. List, O. Beiträge zur Kenntnis des Embolie bei offenem Foramen ovale. Inaug. Diss. Giessen, 1910
- 28. GIEPEL. Paradoxer Embolus in offenem Foramen ovale. München med. Wchnschr., 59: 1683, 1912.
- 29. Kunckel. Paradoxe Embolie. Diss. Warburg, 1912.
- ABRIKOSSOFF, A. J. Zur Casuistik der Parenchymembolien: Kleinhirngewebeembolie der Arteria coronaria cordis beim Neugeborenen. Zentralbl. f. alleg. path. u. path. Anat., 24: 244, 1913.
- HANNEMANN. Thrombus in Foramen ovale. Deutsch. med. Wchnschr., 40: 202, 1914.
- 32. Pous, H. Paradoxer Embolie bei Fraktur. Deutsch. Ztschr. f. Chir., 133: 385, 1915.
- SPECHT. Granatsplitter im linken Ventrikel nach Verletzung der Vena femoralis. München. med. Wehnschr., 64: 892, 1917.
- 34. Hensel, R. Zur Kasuistik der postoperativen paradoxen Embolien im grossen Kreislauf bei offnem Foramen ovale. *Deutsche med. Wchnschr.*, 47: 625
- 35. EISELBERG. In Berichte aus chirurgischen Gesellschaften. Zentralbl. chir., 51: 518, 1924.
- Gold. In Berichte aus chirurgischen Gesellschaften. Zentralbl. chir., 51: 518, 1924.
- 37. Schöning, A. Ueber die retrograde Embolie und Thrombose in den Nebennieenvenen, ihr Zustandekommen und ihre Diagnose. Beitr. z. path. Anat. u. z. alleg. Path., 72: 580, 1924.
- 38. Ranzi. In Berichte aus chirurgischen Gesellschaften. Zentralbl. f. Chir., 51: 518, 1924.
- Schuberth. In Vereinigung der pathologischen Anatomen Wiens. Wien. klin. Wchnschr., 37: 862, 1924
- BEATTIE, W. W. Paradoxical embolism associated with two types of patent foramen ovale. *Internat.* A. M. Museums Bull., 11: 64, 1925.
- 41. DIETRICH, A. Thrombopathie mit parietaler Herzthrombose und paradoxer Embolie. Virchows Arch. f. path. Anat., 254: 830, 1925.

- MÜLLER, H. K. Zur Kenntnis der Emboli und thrombotischen. Verschlusses der Bauchaorta. Inaug. Diss. Marburg, 1925.
- 43. Wittig, M. Ueber die Sog. "Paradoxe Embolie." Ztschr. f. Kreislaufforschung, 19: 505, 1927.
- BARNARD, W. G. A case of paradoxical embolism with a blood clot lodged in the Foramen ovale. Quart. J. Med., 23: 305, 1929.
- WILSON. Cited by Thompson, T. and Evans, W. Paradoxical embolism. Quart. J. Med., 23: 135, 1929.
- WINKELBAUER, A. and Urban, K. Ueber gekreuzte Embolie bei offenem Foramen ovale. Wien. klin. Wchnschr., 42: 1072, 1929.
- THOMPSON, T. and EVANS, W. Paradoxical embolism. Quart. J. Med., 23: 135, 1929.
- Elliott. Cited by Thompson, T. and Evans, W. Paradoxical embolism. Quart. J. Med., 23: 135, 1929.
- Dahl-Iverson. Cited by Hartfell, S. J. Paradoxical embolism of the basilar artery. *Lancet*, 1: 700, 1931.
- 50. French, L. R. Paradoxical embolism. Arch. Path., 11: 383, 1931.
- 51. GIEPEL, P. Zur Kenntnis der Embolism in Herzen. Virchows Arch. f. path. Anat., 282: 67, 1931.
- HARTFELL, S. J. Paradoxical embolism of the basilar artery. *Lancet*, 1: 700, 1931.
- 53. Rabinowitz, M. A., Weinstein, J. and Marcus, I. H. Brain abscess (paradoxical) in congenital heart disease. *Am. Heart J.*, 7: 790, 1932.
- TAYLOR, J. Paradoxical embolism: report of a case. Arch. Path., 16: 901, 1933.
- MERKEL. Über die Bedeutung der sog. Paradoxen oder gekreuzten Embolie für gerichtliche Medizin. Deutsche Ztschr. f. d. ges. gerichtl. Med., 23: 338. 1934.
- 56. Нікschвоеск, F. J. Paradoxical embolism. *Am. J. M. Se.*, 189: 236, 1935.
- Jones, R. A case of paradoxical embolism. *Brit. M. J.*, 2: 225, 1936.
- KORITSCHONER, R. Paradoxical embolism. J. A. M.: A., 106: 1269, 1936.
- Neely, J. M. Paradoxical embolus. Nebraska State M. J., 21: 61, 1936.
- Open foramen ovale and its role in so-called paradoxical embolism. Finska läk-sällsk handl., 80: 937, 1937.
- Ingham, D. W. Paradoxical embolism. Am. J. M. Sc., 196: 201, 1938.
- 62. HANNA, R. Cerebral abscess and paradoxical

- embolism associated with congenital heart disease. Am. J. Dis. Child., 62: 555, 1941.
- Nystrom, G. Cited by Vimtrup, B. Patent foramen ovale and paradoxical embolism. Nord. med., 10: 1839, 1941.
- PORTER, A. G. Paradoxical cerebral embolism. Lancet, 2: 634, 1941.
- VIMTRUP, B. Patent foramen ovale and paradoxical embolism. Nord. med., 10: 1839, 1941.
- Birch, C. A. Paradoxical embolism. *Brit. M. J.*, 2: 727, 1945.
- 67. Young, R. L., Derbyshire, R. C. and Cramer, O. S. Paradoxical embolism. *Arch. Path.*, 46: 43, 1948.
- v. Hofmann, K. Vier Fälle von Strumametastasen im Knochen. Wien. klin. Wchnschr., 10: 1004, 1897.
- BUHLING, W. H. Generalized tuberculosis with patent foramen ovale as a factor in its production. *Am. J. M. Sc.*, 128: 992, 1904.
- Fremberg, C. Die Fettembolie des grossen Blutkreislaufes und ihre Ursachen. Mitt. a. d. Grenzgebieten d. Med. u. Chir., 26: 23, 1913.
- ABBOTT, M. E., LEWIS, D. S. and BEATTIE, W. W. Pulmonary stenosis, ventricular septal defect, and paradoxical embolism. Am. J. M. Sc., 165: 636, 1923
- 72. Pamperl, R. Komplikation bei Strumektomien. Beitr. z. klin. Chir., 132: 680, 1924.
- Armand-Delille, P. and Lesobre, R. Malformation congénitales du coeur avec cyanose; endocardite subaiguë; double hemiplégie. Bull. Soc. pédiat. de Paris, 33: 274, 1935.
- 74. SWANN, R. C. and MERRILL, J. P. Clinical course of acute renal failure. *Medicine*, 32: 215, 1953.
- MERRILL, J. P. The Treatment of Acute Renal Failure. New York, 1955. Grune & Stratton.
- HAGGART, G. E. and WALKER, A. M. Physiology of pulmonary embolism as disclosed by quantitative occlusion of the pulmonary artery. *Arch. Surg.*, 6: 764, 1923.
- 77. MacCanon and Horvath, S. M. Some effects of serotonin in pentobarbital anesthetized dogs. *Am. J. Physiol.*, 179: 131, 1954.
- JACOBI, M., KENLER, M. and SILVERMAN, I. Paradoxical embolism of the coronary artery. Am. Heart J., 9: 414, 1933.
- 79. WOLFF, L. and WHITE, P. D. Acute coronary occlusion. Boston M. & S. J., 195: 13, 1926.
- 80. Saphir, O. Coronary embolism. Am. Heart J., 8: 312, 1933.
- Johnson, B. I. Paradoxical embolism. J. Clin. Path.,
 4: 316, 1951.

Unusual Manifestations in a Case of Relapsing, Nodular, Febrile Panniculitis (Weber-Christian Disease)*

LEONARD M. GOLDBERG, M.D. and LEONARD W. RITZMANN, M.D. Portland, Oregon

The syndrome of relapsing, nodular panniculitis has been considered a disease entity since Weber's [7] case report in 1925, although the disease was first recognized in 1892 by Pfeifer [2]. It was Christian [3] in 1928 who observed that the disease was also characterized by fever and added the term "febrile." In 1936 Brill [4] first referred to this entity as "Weber-Christian" disease. Although the number of reported cases has increased in recent years, the total remains less than 100 cases [5,6].

The diagnosis is based on the history of recurrent crops of raised, nodular, subcutaneous lesions, 0.5 to 10 cm. in diameter, which may be painless or tender. The overlying skin is often red, but may be normal. The lesions tend to regress slowly over weeks or months leaving areas of subcutaneous atrophy with pitting and frequently hyperpigmentation. The fat early is infiltrated by mononuclear cells, with phagocytosis by macrophages. Foreign body giant cells and fat-laden macrophages (foam cells) are present. Later there is atrophy of the subcutaneous tissue and replacement by fibrosis. Although most of the reported cases have not shown suppuration, in several the nodules have developed liquefaction. Recently it has been shown that the disease process is not restricted to the panniculus adiposus but involves the fat tissues scattered throughout the entire body. Steinberg [7], in reviewing six autopsy cases from the literature and adding two of his own, found the typical histologic lesions in the omental, mesenteric, perirenal, periadrenal and pericardial fat. There were also areas of patchy fibrosis and fat necrosis in the bone marrow and focal areas of necrosis in the liver. In one case report [8] bone was shown to be involved, with destructive

changes of the shaft and cortex of phalanges in two fingers and a toe.

The present case is submitted because of its unusual manifestations and marked involvement of bone. Repetitive hospitalizations have been necessary for therapy of many suppurative lesions. The diagnosis was made during hospitalization for an acute myocardial infarction.

CASE REPORT

A thirty-nine year old white male laboratory assistant entered the Veterans Administration Hospital, Portland, Oregon, for his sixteenth hospitalization in the past nine years because of a sudden episode of fainting. It came without warning while the patient was at work. No one witnessed his fall but he was found lying unconscious immediately thereafter by several observers. After two to three minutes he revived spontaneously and complained only of severe pain in the right hip (a locus of chronic disease for many years). He had no chest pain, dyspnea, headache, dizziness, blurred vision or palpitation, and no previous syncope or aura. He was hospitalized for observation.

The patient was last completely well in 1948 when he fell from an apple box a distance of 3 feet and landed on his right hip. The following day he noted severe pain in the hip and consulted a physician but was told there were no x-ray abnormalities. Because the pain became increasingly severe, a local orthopedic surgeon recommended hospitalization. At that time the area of his right hip was needled and a large amount of greenish gray "pus" aspirated. The site of needling continued to drain for approximately ten days. The patient was then transferred to the Veterans Administration Hospital in Vancouver, Washington, for further therapy of the draining hip. On admission, examination showed only a fluctuant swelling over the greater trochanter of the right hip, an increased erythrocyte sedimentation rate and a moderate anemia. Needle aspiration of the hip yielded a moderate amount of seropurulent drainage. Smears

^{*} From the Department of Medicine, Veterans Administration Hospital, Portland, Oregon.

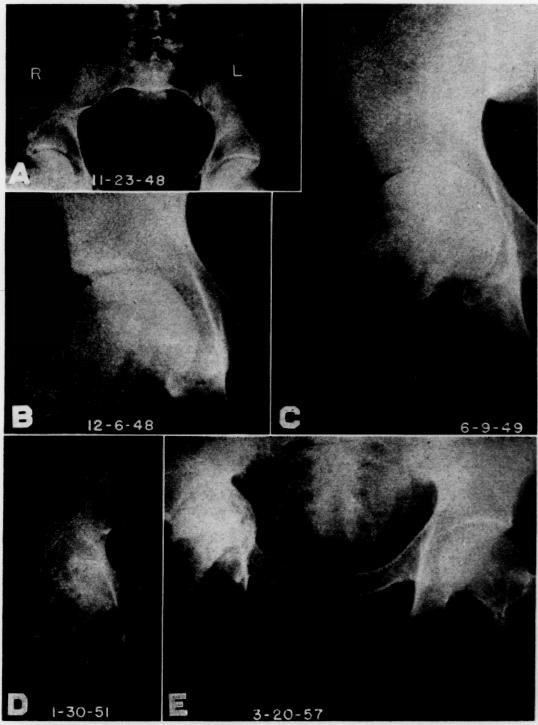


Fig. 1. A, roentgenogram of pelvis (November 23, 1948) reveals normal hip joints bilaterally. B, roentgenogram of right hip (December 6, 1948) shows narrowing of the joint space and loss of sharp margination of the superomedial outline of the acetabulum. C, roentgenogram of right hip (June 9, 1949) demonstrates further progression with drifting of the femoral head medially. D, roentgenogram of right hip (January 30, 1951) reveals sclerosis and eburnation of acetabular margin with beginning protrusion of femoral head. E, roentgenogram of pelvis (March 20, 1957) shows further deepening of the acetabulum with superior and medial displacement of the femoral head; this now is a well developed protrusio acetabuli.

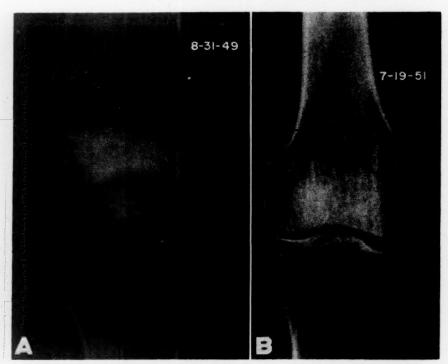


Fig. 2. Anteroposterior views of right knee. A, August 31, 1949, demonstrates demineralization of the ends of the femur and tibia. B, July 19, 1951, depicts remineralization with coarse trabecular pattern.

and cultures of the aspirate were negative for pyogenic organisms, fungi and acid-fast bacilli. Intermediate strength PPD was negative. He was placed in a bilateral hip spica plaster cast, treated with courses of streptomycin and chloromycetin,® and discharged in the cast after approximately eight months of hospitalization. Two weeks later the patient stumbled and fractured his right fifth toe, for which he was readmitted. After four days a red, hot, swollen area developed in the web between the fourth and fifth toes but subsided after administration of hot packs and penicillin therapy. One week later the patient twisted his right knee. This became red, hot and swollen, and aspirations yielded a greenish gray "pus" from which neither pyogenic organisms nor acid-fast bacilli could be cultured. The inflammation subsided after treatment with penicillin, hot packs, and rest. When the hip spica was removed after nine months the patient was left with only 10 to 15 per cent motion in the right hip and also some restricted movement of the right knee.

After these initial difficulties the patient continued to have frequent swellings of both knees and of the right ankle, always associated with minor trauma such as twisting, "straining" or bumping. In addition, he had recurrent episodes of red, hot, tender swellings of the skin of various parts of his body, also associated with trauma often of a very minor degree such as leaning against a ladder or lying on a hard object. The skin lesions took the form of raised, firm, tender nodules most commonly located in exposed areas on both lower extremities, both arms and forearms. On

six occasions he was hospitalized for incision and drainage of skin swellings, and greenish gray material similar to the joint aspirates was recovered. This "pus" was always sterile for pyogenic organisms, fungi and acid-fast bacilli. A few lesions spontaneously drained. Frequently, however, the lesions resolved and disappeared spontaneously, leaving residual areas of hyperpigmentation and depression of skin. During the acute episodes his maximum temperature elevations ranged from 99° to 102.5°F.; white blood cell counts varied from 5,000 to 16,500 per cu. mm., frefrequently with eosinophilia from 7 per cent to 19 per cent; Westergren erythrocyte sedimentation rates usually averaged between 25 and 40; repeated coccidioidin skin tests were positive in dilutions of 1:100, but two separate complement fixation tests were negative. Several liver function panels were normal as was an electrophoretic pattern of protein in both serum and joint fluid. Bone marrow aspiration was normal on one occasion.

Serial radiographs of his hip since the original injury showed an initial narrowing of the joint space between the femoral head and the acetabulum with subsequent weakness and invagination of the floor of the acetabulum. (Fig. 1.) The femoral head was displaced medially producing a unilateral Otto-Chrobak pelvis (protrusio acetabuli). Over several years this progressed to a rather marked degree, but except for slight molding of the femoral head all the radiological changes were limited to the acetabulum. Serial x-rays of the right knee (Fig. 2) showed rather extensive

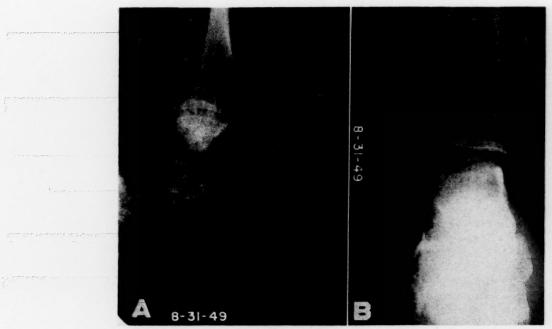


Fig. 3A and B. Lateral and anteroposterior views of right ankle (August 31, 1949) showing spotty demineralization of the distal tibia and fibula and demineralization of the bones of the ankle and foot.



Fig. 3C and D. Lateral views of right and left ankles (July 2, 1957) showing remineralization with coarse trabeculae in right ankle compared to left ankle.

demineralization of the bone surrounding the joint, with a subsequent irregular return of calcium to these areas and production of coarse trabecular striations. Similar changes were also seen in the right ankle. (Fig. 3.)

Physical examination revealed a pale, diaphoretic young adult white male of slight build. The temperature was 100°F., pulse 110 and regular, respirations 20, and blood pressure 140/110 mm. Hg. Eyes, ears,

nose and throat were negative for abnormalities except for moderate injection of the pharynx. The chest was clear to auscultation and percussion. The heart was not enlarged and there were no murmurs, rubs or thrills. The heart tones were snapping. There was no abdominal tenderness; organs or masses could not be felt. The right hip was markedly painful with approximately 5 to 10 degrees of motion at the hip joint. On the skin of the legs, thighs and arms there were

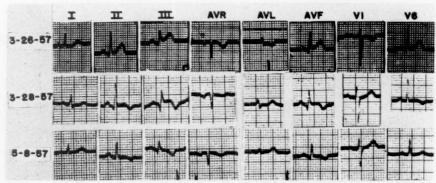


Fig. 4. Electrocardiogram dated March 26, 1957, taken two hours after onset of chest pain, showing elevation of S-T segments in leads AVF, II, III. Serial tracings dated March 28, 1957 and May 8, 1957, showing well developed Q waves and ST-T changes typical of the evolution of an acute posterior myocardial infarction.

multiple irregular areas of hyperpigmentation with depression of the skin. On palpation of these areas there seemed to be atrophy of the subcutaneous tissue. Neurological examination was normal.

Laboratory data included a white blood cell count of 9,400 per cu. mm. with 70 per cent polymorphonuclear leukocytes, 2 per cent band cells and no eosinophils. The erythrocyte sedimentation rate was 9 mm. per hour by the Wintrobe method; hematocrit, 49 per cent; blood urea nitrogen, 12.6 mg. per cent; icteric index, 5; report from Venereal Disease Research Laboratories, negative; urinalysis, normal. The serum total protein was 7.1 gm. per cent with 4.6 gm. per cent albumin and 2.5 gm. per cent globulin. The serum total cholesterol was 268 mg. per cent and total lipids, 466 mg. per cent. Serum electrolytes were normal. Electroencephalogram was interpreted to be within normal limits.

The patient was kept at bedrest. His temperature rose to 101.6°F. on the day after admission, then gradually dropped over the next five days to normal levels where it remained throughout the course of his hospitalization. Blood cultures and repeated examinations failed to reveal any obvious cause for the fever. On March 25, 1957 (five days after admission) the patient had a fifteen-minute episode of "knot-like" squeezing, substernal pain with slight radiation down the left arm. Electrocardiogram taken two hours after onset of pain showed early changes of an acute posterior myocardial infarction with slight elevation of the S-T segments in leads AVF, 11 and 111. (Fig. 4.) Subsequent serial electrocardiograms demonstrated the typical evolutionary changes of an acute posterior myocardial infarction. There was no subsequent episode of chest pain and no cardiac complications developed.

During this hospitalization Weber-Christian disease was suspected for the first time as the possible etiology for his chronic recurring illness. Since the biopsy of a subcutaneous lesion was needed for diagnosis, and no new lesions were now present, the patient obligingly

attempted to produce a lesion with trauma by striking himself a blow on the left leg with a reflex hammer. Two days later, in the area of the trauma, there was noticeable redness, induration, swelling and tenderness which increased in severity in the next four days, by which time fluctuation was present. During the next five to seven days, three other lesions appeared following minimal trauma; one developed on his back where he had fallen asleep and lay on the radio earphones. A biopsy of the hammer-induced lesion showed the microscopic picture of panniculitis (Fig. 5). There was extensive infiltration composed of neutrophils, histiocytes and proliferating fibroblasts, as well as many fat-laden macrophages. Scattered throughout were multinucleated foreign body giant cells. There was one area of extensive neutrophilic infiltration characteristic of a suppurative inflammatory abscess. The histologic picture was considered by our pathologist to be compatible with the diagnosis of Weber-Christian disease.

Comment: This case exhibits the features considered diagnostic of Weber-Christian disease—a chronic febrile illness with recurrent subcutaneous inflammatory nodules which histologically show the classic picture of fat necrosis and in healing leave atrophy, pitting and hyperpigmentation of the skin. In addition there are several aspects worthy of separate consideration.

First, every lesion which appeared in this patient followed trauma, however mild or insignificant. In the pathogenesis of Weber-Christian disease many different etiologic agents have been incriminated in individual cases, including ingestion of halogen compounds, systemic infections, exposure to cold and mechanical trauma, but some have had no apparent inciting agent. Bendel [9] has believed that many "spontaneous lesions" could be related

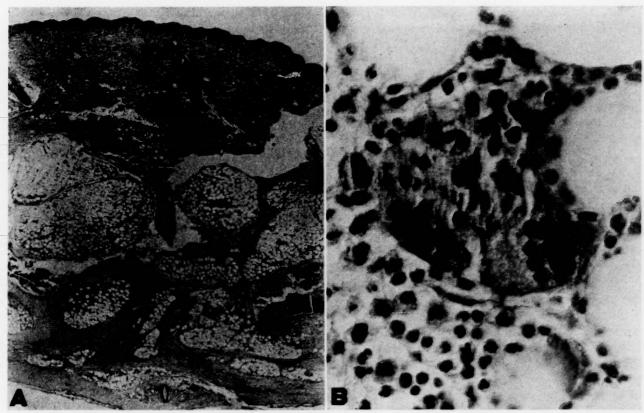


Fig. 5. A, photomicrograph of biopsy of acute lesion. Normal epidermis is demonstrated with infiltration of subcutaneous fat layers. Necrosis with abscess formation is seen in lower right corner. B, high power view shows the fat infiltrated with many neutrophils, vacuolated histocytes and multinucleated foreign body—type giant cells.

to previous inapparent trauma. This proved to be true in this patient in whom one lesion appeared in an area where he had merely lain on a hard object.

Second, the lesions in our patient frequently underwent liquefaction although the inflammatory process of Weber-Christian disease is classically considered to be unassociated with fluctuation. However, Weber's second case [10] and those of several others [9,11] did show suppurative inflammation with "pus" described variously as light yellow, pale green or greenish gray matter composed of sterile cellular debris or an amorphous material. The disease process follows some stimulus which produces a metamorphosis in the fat tissue, the fat then acting as a foreign body and provoking a typical foreign body reaction. Bendel [9] believes that the suppurative reactions merely represent a more severe phase of the inflammatory response.

The fat necrosis of this disorder seems most closely to approach that type found in the breast associated with suppurative disease, carcinoma or other causes of pressure ischemia (e.g., biopsy-surgery), with the typical histologic

picture of panniculitis. The fat necrosis which occurs following pancreatic enzyme release is due to digestion of fat in the omentum and other intra-abdominal viscera with the liberation of fatty acids. This eventually produces thin, whitish, opaque nodules. Calcium tends to be deposited in these areas and causes a secondary foreign body reaction. The fat necrosis seen in insulin lipodystrophy is characterized by a localized loss of fat in areas where insulin has been injected. Here the adipose tissue disappears without an active inflammatory response.

A third unusual feature of this patient's clinical picture is the extensive bone involvement. Steinberg [7] published cases showing patchy fibrosis and fat necrosis in the bone marrow but involvement of bone cortex is reported in only one other case [8], in which x-rays demonstrated destructive cystic changes in the shaft and cortex of the phalanges of an index finger and thumb, and in the metatarsophalangeal joints of a toe. The toe was later amputated because of severe persistent pain, and the histologic section showed fat necrosis in the marrow with adjacent fibrosis and infiltration by lympho-

cytes, macrophages and multinucleated giant cells. In our patient serial roentgenograms have demonstrated the evolution of a typical protrusio acetabuli. In this abnormality [12] destruction and weakening of the acetabular floor results in invagination of the acetabulum and medial displacement of the femoral head. Subsequently reactive new bone formation occurs. This relatively rare condition is usually associated with an inflammatory process which is localized to the acetabulum but spares the femoral head. The hip deformity in our patient followed his accidental fall in 1948. It is assumed that the trauma of the fall produced inflammatory necrosis in the synovial fat (haversian glands) of the acetabulum. This severe inflammatory condition then caused destruction of the acetabular floor with the production of the protrusio acetabuli.

The early radiographs of the knee demonstrate definite demineralization of the distal end of the femur and proximal tibia. Serial films show a return of calcium, but in heavy, coarse, irregular striations differing from the recalcification following demineralization of bone by disuse. The latter is usually fine and regular and gives a normal appearance to the recalcified bone. The coarse, irregular trabeculations could result from recalcification of areas of bone underlying the inflammatory process in the synovial fat. The characteristic manner in which the acute condition of the joints developed in our patient following trauma conforms to the pattern of development of his subcutaneous lesions. Although it was desirable to take a biopsy of one of the patient's involved bones, it was thought inadvisable to perform such surgery for fear of producing prolonged drainage such as followed his previous hip trauma.

The final feature is the myocardial infarction. The patient is a rather slightly built, thirtynine year old male with normal blood cholesterol and lipids. Hospitalization was prompted by a syncopal episode with no apparent cause. The following day fever to 101.6°F. developed, gradually dropping over the next five days. No obvious cause for this temperature elevation was apparent. On the fifth day after admission severe retrosternal pain occurred and an electrocardiogram showed the changes of a very acute posterior myocardial infarction. The electrocardiographic abnormalities were more acute than one would expect if the myocardial infarction had precipitated his syncopal attack five

days previously. The changes are more typical of an area of myocardial infarction developing within a few hours prior to the recording of the electrocardiogram. Perhaps when the patient fell during his fainting episode there was sufficient trauma to the pericardial fat to result in inflammatory fat necrosis. The inflammation could have caused a contiguous angiitis of a coronary vessel traversing the area with a resultant inflammatory occlusion and myocardial infarction. The mild fever, then, early in his hospitalization did not necessarily represent myocardial necrosis but could have been the usual febrile reaction to his inflammatory process. Although this explanation obviously is pure speculation it remains a possibility.

SUMMARY

A case of relapsing, nodular, febrile panniculitis (Weber-Christian syndrome) is presented. Trauma was the inciting etiologic factor of the patient's lesions, many of which underwent liquefaction. This case is unusual in manifesting marked bone involvement.

Acute myocardial infarction, which occurred in this patient, is considered as a possible rare

complication of the disease.

Acknowledgments: We wish to express sincere appreciation to Dr. Loren W. Stille for his interpretation of the x-rays, to Dr. Ernest J. Losli for analysis of the pathological specimen, to Mr. Dean Altman for producing all the illustrations, and to Miss Kaye Maloney for secretarial help.

REFERENCES

1. Weber, F. P. A case of relapsing non-suppurative nodular panniculitis, showing phagocytosis of subcutaneous fat cells by macrophages. Brit. J. Dermat. & Syph., 37: 301-311, 1925.

2. PFEIFER, V. Ueber einen Fall von herdweiser Atrophie des subcutanen Fettgewebe. Deutsches

Arch. klin. Med., 50: 438, 1892.

3. Christian, H. A. Relapsing, febrile, nodular, nonsuppurative panniculitis. Arch. Int. Med., 42: 338-

351, 1928.

4. Brill, I. C. Relapsing febrile nodular non-suppurative panniculitis (Weber-Christian disease). In: Medical Papers Dedicated to H. A. Christian, pp. 694-704. Baltimore, 1936. Waverly Press, Inc. 5. BEERMAN, H. Weber-Christian syndrome. Am. J. M.

Sc., 225: 446, 1953.

6. HALLAHAN, J. D. and KLEIN, T. Relapsing, febrile, nodular, non-suppurative panniculitis (Weber-Christian disease); review of literature and report of case. Ann. Int. Med., 34: 1179-1201, 1951.

- 7. Steinberg, B. Systemic nodular panniculitis. Am. J. Path., 29: 1059, 1953.
- Delor, C. J. and Martz, R. W. Weber-Christian disease with bone involvement. Ann. Int. Med., 42: 451, 1955.
- Weber, F. P. A further note on relapsing febrile, nodular, non-suppurative panniculitis. Brit. J. Dermat. & Syph., 47: 230, 1935.
- 11. Shaffer, B. Liquefying nodular panniculitis: report of a case. Arch. Dermat. & Syph., 38: 535, 1938.
- Schinz, H. R., Baensch, W. E., Friedl, E. and Uehlinger, E. Roentgen-Diagnostics, vol. 2, part 2, p. 1047. New York, 1952. Grune & Stratton.

Pulmonary Infiltration with Eosinophilia and the Alveolar-Capillary Block Syndrome*

Frederic Eldridge, m.d. †

San Francisco, California

Löffler [7] first reported the association of pulmonary infiltrations and blood eosinophilia in 1932. Since that time many cases with this combination of findings have been reported; in 1952 Crofton [2] found over 450 in the literature. These patients have had quite variable clinical courses and symptoms, ranging from a short benign illness (as in Löffler's cases) to a prolonged course with severe symptoms [2,3]; in some cases the outcome has even been fatal [4].

Malaise, cough, sputum and pain in the chest are the common symptoms in the more benign cases, high fever, asthmatic wheezing, dyspnea and bloody sputum occur less frequently. Cyanosis has been described in only a few cases. In some patients, it occurred terminally after a long illness; in others, there was apparent bronchospasm with airway obstruction; and in a few, the clinical findings suggested the presence of a gas diffusion abnormality. In none of these patients, however, have studies been made in an attempt to delineate the physiologic abnormality.

The present case is being reported because of the very severe symptomatology, the relatively short course followed by complete recovery, and the clinical and physiologic evidence of the alveolar-capillary block syndrome.

CASE REPORT

E. J., a sixty-eight year old woman, entered Stanford University Hospitals on September 23, 1956, because of increasing fatigue and dyspnea of about two weeks' duration. Since childhood she had suffered recurring mild eczematoid dermatitis mainly involving the hands and legs, but on two occasions (in 1943 and in 1948) a generalized, red, weeping skin eruption had developed following parenteral injections. Complete clearing of the skin lesions had occurred on each occasion after two to three months.

In 1955 a scaling rash appeared on the palmar

aspect of each hand. This skin disorder had persisted in spite of many treatments with various therapeutic agents, including coal tar, vioform, superficial fractional x-rays, cold quartz radiation, intravenous calcium, and perhaps others unknown.

One week prior to hospital entry she had received injections of hydrocortisone into the palmar areas. She had noted the onset of weakness and fatigue one week before this, but on the day following the injections she had experienced a definite increase in the fatigue and malaise, and marked dyspnea on exertion had developed. During the succeeding week, progressive worsening of the dyspnea had occurred, pain in the chest had developed, and cyanosis had appeared. She entered the hospital on the fifteenth day of respiratory illness. There had been no peripheral edema, orthopnea, palpitation, fever or muscle pain, and no past history of asthma or other pulmonary disease was elicited.

On physical examination her appearance was that of a very ill elderly woman with striking cyanosis of lips and nail beds. She would become markedly dyspneic on the slightest exertion, and even the act of talking provoked dyspnea. Tachypnea (32 to 34 breaths/minute) was present at rest. The pulse rate was 80/minute. Blood pressure was 130/80 mm. Hg. The temperature was 37°c. and remained within the normal range throughout the hospital stay. Symmetrical hyperkeratoses of both palms were accompanied by some scaling of the sides and dorsa of the fingers. There was no venous distention or peripheral edema. Breath sounds were of normal quality, but numerous crackling rales were heard in the lower lung fields bilaterally. The heart size, rhythm and sounds were within normal limits, as was the remainder of the examination.

Laboratory studies revealed a hematocrit of 43 per cent, hemoglobin of 14.4 gm./100 cc., erythrocyte count of 4.0 million/cu. mm., erythrocyte sedimentation rate of 18 mm./hour, and white cell counts ranging between 10,000/cu. mm. and 11,000/cu. mm. There was definite elevation of the eosinophil count. (Table I.) The urine was normal on several occasions. A serologic test for syphilis was non-reactive. Serum

^{*} From the Department of Medicine of the Stanford University School of Medicine, San Francisco, California.

Supported in part by a grant from the San Francisco Heart Association.

† Scholar in Medical Science of the John and Mary R. Markle Foundation.

TABLE I
WHITE CELL AND DIFFERENTIAL BLOOD COUNTS

Direct Count	Time of Illness								
Blood Count	15 days	16 days	21 days	30 days	6 mo.				
White blood cells/cu. mm.	10,000	10,550	11,000	10,500	10,300				
Eosinophils (%)	2,300 23	2,105 20	1,485 13.5	1,470 14	55				
Neutrophils (%)*		58 [3]	60 [6]	68 [3]	65.5 [1]				
Lymphocytes (%)	17	14	15	15	17				
Monocytes (%)	9	. 8	8.5	3	7				
Basophils (%)			- 3						

^{*} Figures in brackets represent percentage of banded forms.

creatinine was 1.1 mg./100 cc. The total protein level was 7.6 gm./100 cc. with a normal albumin and globulin, and the electrophoretic pattern was within normal limits. A stool examination demonstrated no ova or parasites.

The venous pressure was 6.2 cm. of water above the mid-chest. Arm to tongue circulation time was eleven seconds. An electrocardiogram on admission (fifteenth day of illness) showed a distinct change from the patient's previously normal record in that the T waves in Leads 1 and V3-6 had become lower. An intradermal tuberculin test was positive with a second strength PPD. A histoplasmin test was negative. Sputum culture revealed normal nasopharyngeal flora. Only one eosinophil was seen on a smear of the

X-ray examinations of the chest taken on the fifteenth, nineteenth and thirtieth days of illness showed essentially the same findings. Those of the thirtieth day are shown in Figures 1 and 2 and were interpreted as follows: "There is a bilateral increase in the interstitial markings of the lungs, most marked in the lower lung fields, but involving all segments of both lungs. In addition, a number of punctate densities are noted bilaterally. The reticular pattern resulting from the increased interstitial markings is strongly suggestive of widespread interstitial fibrosis."

The results of pulmonary function studies performed on the twenty-fourth day of illness are detailed in Tables II and III.

Digitalization with whole leaf soon after the patient's hospital admission was without apparent



Fig. 1. X-ray of the chest taken on the thirtieth day of illness showing bilateral increase in interstitial markings of the lung fields.

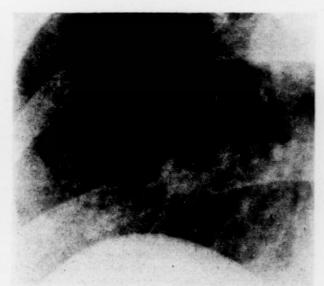


Fig. 2 Enlarged view of the right lower lung field of the chest x-ray taken on the thirtieth day of illness. There is a reticular pattern resulting from the diffuse increase in interstitial markings.

TABLE II
PULMONARY FUNCTION TESTS

Tests	Time of Illness					
1 ests	24 days	6 mo.	Predicted			
Vital capacity (cc.). Timed expiratory capacity (% of vital capacity)	1295	2540	2700			
1 sec	100	78	>75			
3 sec		97	>95			
Maximum breathing capacity (L./min.)	*	123	104			
Compliance of chest and lungs (L./cm. H ₂ O)	0.055		0.100			
			1			

Note: See Note under Table III.

* Patient too ill to perform this test.

benefit and was subsequently discontinued. During administration of oxygen by mask there was complete relief of cyanosis and of the symptoms of weakness and dyspnea

With no additional treatment there was gradual symptomatic improvement beginning on the twenty-eighth day of illness. This was accompanied by a lessening of cyanosis and arterial hypoxemia. Pulmonary function studies performed on the thirtieth day of illness (Table III) showed slight improvement. By the thirty-fifth day of illness, cyanosis had further decreased and the patient incurred only moderate fatigue and dyspnea when walking around the ward. She was discharged to her home on the thirty-ninth day of illness, October 18, 1956.

She subsequently continued to improve. When seen again in March 1957 she was feeling very well, and

TABLE III
PULMONARY FUNCTION TESTS*

	Time of Illness				
Tests	24 days	30 days	6 mo.	Normal	
Respiratory rate/min.	36	30	20	15-20	
Minute volume (L./min.)	15.7	12.4	7.2	7.0	
Tidal volume (cc.)	436	413	360	350-500	
Physiologic dead space (cc.)		164	147	140	
Alveolar ventilation (L./min.)		5.7	2.6	3.0	
Oxygen uptake (cc./min.)	280	238	192	200	
Respiratory exchange ratio	0.81	0.99	0.80	0.80	
O ₂ Saturation (%) Rest	75	80	93	95	
Exercise.	64	72	95	95	
100% O ₂	101†	102†	104†	106†	
pO ₂ (mm. Hg)		42	†	90	
CO ₂ content (cc./100 cc.)	42.7	45.3	48.5	48-50	
pH	7.50	7.47	7.35	7.40	
pCO ₂ (mm, Hg)	29	32	44	38-42	
Alveolar pO ₂ (mm. Hg)	116	118	96	100	
Alveolar-arterial O2 gradient (mm. Hg)	79	76	‡	10	

Note: Vital capacity and timed expiratory capacity were measured with a 6-L. recording spirometer. The maximum breathing capacity was determined by collecting the expired air for fifteen seconds in a neoprene bag and measuring this volume in a gas meter. The compliance of chest and lungs was measured by a technic similar to that described by Heaf and Prime [24]. Ventilation and gas exchange studies were performed with the patient supine. Expired air was collected in a Tissot gasometer, and its composition analyzed in a Scholander apparatus. Arterial blood oxygen content and capacity and carbon dioxide content were determined in the Van Slyke apparatus. Arterial blood pH was determined in a Cambridge Research Model pH meter at a temperature of 37°c. The partial pressure of carbon dioxide was calculated from the carbon dioxide content and pH by means of the nomogram of Singer and Hastings [25]. The partial pressure of oxygen in arterial blood was calculated from the oxygen saturation and pH by means of the nomogram of Guest [26]. The physiologic dead space was calculated from the Bohr formula, substituting arterial blood pCO₂ for alveolar pCO₂. The alveolar partial pressure of oxygen was calculated from the alveolar air equation making the same substitution. Ventilatory volumes are expressed as BTPS. Other gas volumes are expressed as STPD. Predicted and normal values for all determinations are average values as determined in this laboratory or from other sources [27].

* All values are for rest breathing air unless otherwise noted.

† Includes dissolved oxygen.

Not possible to calculate.

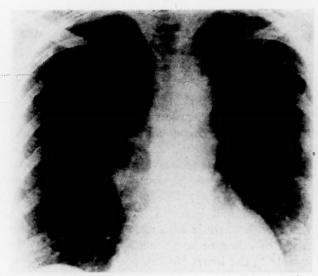
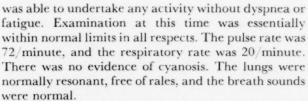


Fig. 3. X-ray of the chest taken six months after the onset of illness showing the decrease of interstitial markings as compared to Figure 1.



Hematologic studies revealed an hematocrit of 40 per cent, hemoglobin of 13.8 gm./100 cc., and a white cell count of 10,300/cu. mm. The differential white count was in the normal range with less than 1 per cent eosinophils. (Table 1.) A stool examination was again negative for ova and parasites. An electrocardiogram showed a return of the T waves to their previously normal appearance.

X-ray films of the chest at this time (Figs. 3 and 4) were interpreted as follows: "There has been complete clearing of the increased interstitial densities present in the previous examinations, and, except for the punctate densities previously described (probably the result of old histoplasmosis), the lungs appear normal for a woman of this age." Pulmonary function studies (Tables II and III) revealed normal findings in all respects.

One year after her acute illness, her own physician reported that she continued to enjoy good health.

COMMENTS

The alveolar-capillary block syndrome has been described in a variety of conditions with fibrous, granulomatous or inflammatory involvement of the alveolar-capillary septums [5–7], resulting in impairment of diffusion of gases across these septums. Certain clinical findings have been considered characteristic of the



Fig. 4. Enlarged view of the right lower lung field of the chest x-ray shown in Figure 3. The interstitial markings are essentially normal in appearance.

syndrome [8], and include diffuse pulmonary involvement, progressive dyspnea, tachypnea at rest and after exercise, cyanosis after exercise, rales at the lung bases, and lack of evidence of bronchial obstruction. The occurrence of this set of findings, as in the present patient, should lead one to suspect the diagnosis of the alveolar-capillary block syndrome.

The physiological characteristics of the syndrome, as given by Cournand [8], include reduced lung volumes, well preserved maximum breathing capacity, hyperventilation at rest and during exercise, normal arterial oxygen saturation and low carbon dioxide tension at rest, marked arterial oxygen unsaturation after exercise, a high alveolar oxygen tension, a reduced oxygen diffusion capacity, and a normal or slightly abnormal ventilation-perfusion relationship.

Although the maximum breathing capacity could not be estimated in the present patient, the complete expulsion of the vital capacity in one second rules out the presence of significant airway obstruction, and makes unlikely an increase in residual volume as the cause of the decreased vital capacity. In the presence of diffuse infiltrative pulmonary disease, the most probable cause of the low vital capacity is increased rigidity of the lungs. This explanation is validated by the finding of a decreased thoracic compliance. The return to a normal vital capacity at six months, after the clearing of the lung

lesions, shows the mechanical change to have been a transient one related to the infiltrative disease.

Although hyperventilation and the resultant low arterial carbon dioxide tension and high alveolar oxygen tension were present in this patient, the arterial oxygen saturation (75 per cent, at rest) was much lower than is usual in the alveolar-capillary block syndrome [6,8,9]. Ideally, in a situation such as this, one would like to have a direct evaluation of the ventilation-perfusion relationships and the diffusion characteristics of the lungs by the Riley technic or by the carbon monoxide method for measuring diffusing capacity. Although this was not possible in this patient, some findings are available for an evaluation of the problem. The physiologic dead space, while not outside normal limits, using the patient after recovery as her own control, was somewhat elevated; and the arterial blood during the breathing of 100 per cent oxygen failed to contain as much dissolved oxygen as expected. These two facts suggest that a ventilation-perfusion abnormality was present.

On the other hand, for the large alveolar-arterial oxygen gradient of 79 mm. Hg to have been caused solely by a ventilation-perfusion abnormality would have required a physiological shunt of almost 50 per cent of the pulmonary blood flow at rest, which seems unlikely. It is much more probable that a diffusion abnormality was responsible for a large part of the arterial unsaturation. The further lowering of arterial oxygen saturation on mild exercise is also better explained by a diffusion abnormality than by an increase in physiological shunt.

In any case, a precise differentiation between distributional and diffusional abnormalities is unimportant. Donald and co-workers [10], for example, have pointed out that a very severe barrier to diffusion may produce the physiological findings of both abnormalities. Marks and his colleagues [9] suggest that "because of the almost constant association of diffusion defects with abnormally large venous admixture, the room air A-a [alveolar-arterial oxygen tension] gradient alone is a significant measurement in patients in whom a diffusion impairment is suspected."

Thus, in patients with very severe diffusion barriers, the arterial saturation may be very low. Such a patient who had diffuse histiocytosis of the lung and alveolar-capillary block, with findings similar to the present case, has recently been reported by Renzetti and others [7].

The eponymic syndrome described by Löffler in 1932 [1] and 1936 [11] consisted of transient shifting pulmonary infiltrations by x-ray examination and an associated blood eosinophilia. Löffler made a point of the lack of severe symptoms and the short course. Although many cases fulfilling the criteria of the original syndrome have been reported, there also have been patients with more severe symptoms and more prolonged courses. These range from patients with prolonged illnesses followed by recovery, those with chronic asthma, those with involvement of other organs such as the skin [12], the eyes [13], the heart [14,15], the stomach [16] and the liver [17], to patients with classic periarteritis nodosa [18].

Many etiologic agents, including parasitic infestations, certain drugs, pollens, and bacterial and food allergies have been associated with pulmonary infiltrations and eosinophilia. However, it is now generally agreed [2,17,19] that all cases, from the classic benign Löffler's syndrome to periarteritis nodosa, have a common pathophysiologic basis, that of a hyperimmune hypersensitivity reaction similar to those experimentally produced in rabbits by Rich and Gregory [20]. Engfeldt and Zetterstrom [19], for example, believe that all degrees of this reaction may occur in man, from a classic Löffler's syndrome to a process characterized by severe vascular lesions, and that there may be changes in a single organ or systemic reactions; and Zuelzer and Apt [17] opine that "Löffler's syndrome becomes a narrow band in the broad spectrum of sensitivity states in which the main 'shock organ' happens to be the lungs."

The term "Löffler's syndrome" has been applied by various authors to all forms of this reaction if a pulmonary infiltrate has been present. However, in view of the variable organ involvement and the variable symptomatology even when a single organ is involved, and in the interest of clarity in communication, it would appear wise to follow the suggestions made by several authors [2,17,19], i.e., to limit the term, Löffler's syndrome, to the benign form of pulmonary infiltrations with eosinophilia as originally described.

The patient reported on here had a definite allergic history; since no infectious disease could be demonstrated, it would appear likely that her illness was on a basis of hypersensitivity. Al-

though it is reasonable to suspect that one of the many therapeutic agents for her skin disease may have been responsible for the development of her illness, no specific agent could be implicated. Her condition seemed to get worse after the injections of hydrocortisone; however, it is clear that her illness had started before these injections were given, and since the adrenal steroids are usually beneficial in this disease, it seems unlikely that the hydrocortisone had any relationship to her illness.

Pathologic studies in mild cases of pulmonary infiltration with eosinophilia have been rare. Meyenburg [21] reported on four patients who died of other causes. There was focal pneumonitis with eosinophils in the alveolar exudate, and eosinophilic infiltration of the vascular walls, but no other evidence of vascular damage. Broch's [22] patient who had had asthma along with marked blood eosinophilia for one year, had an area of consolidation, the alveoli being filled with lymphocytes, plasma cells and eosinophils; and there were eosinophilic infiltrations in the thickened interstitial tissue. Harkavy [23] examined four patients who died of the more severe form of the disease. In these patients he found the pulmonary infiltrations to be areas of congestion with thickened interalveolar septums infiltrated with eosinophils, polymorphonuclear leukocytes and lymphocytes. Blood vessel lesions varied from intimal thickening to acute necrotizing arteritis. The patient of Bayley and coworkers [4] showed similar lesions. Bergstrand's [18] patients all had the lesions of periarteritis nodosa and fibrosis of the lung as well.

Pathological findings such as these would readily explain the development of the alveolar-capillary block syndrome when, as in the present patient, there is widespread and diffuse pulmonary involvement. The complete recovery of this patient suggests that her reaction was one of the intermediate forms which produced reversible widespread interstitial infiltration without necrotizing lesions.

SUMMARY

The clinical and physiological findings of the alveolar-capillary block syndrome were found in a patient who had diffuse pulmonary infiltrations and blood eosinophilia, and who subsequently recovered completely.

The syndrome of pulmonary infiltrations with blood eosinophilia, including the benign Löffler's syndrome, is considered to be due to a hyperimmune hypersensitivity reaction. In view of previously described pathologic findings in this syndrome, it is not surprising to find the alveolar-capillary block syndrome in the present patient whose lungs were diffusely involved.

Acknowledgment: The author acknowledges the assistance of Dr. Marvin B. Bacaner in performing some of the physiologic studies on this patient.

REFERENCES

- LÖFFLER, W. Zur Differential-Diagnose der Lungeninfiltrierungen; über flüchtige Succedan-Infiltrate (mit Eosinophilie). Beitr. z. Klin. d. Tuberk., 79: 358, 1932.
- CROFTON, J., LIVINGSTONE, J., OSWALD, N. and ROBERTS, A. Pulmonary eosinophilia. Thorax, 7: 1, 1952.
- 3. Mark, L. Loeffler's syndrome, with report of 23 cases. Dis. of Chest, 25: 128, 1954.
- BAYLEY, E., LINDBERG, D. and BAGGENSTOSS, A. Loeffler's syndrome; report of a case with pathologic examination of the lungs. Arch. Path., 40: 376, 1945
- BALDWIN, E., COURNAND, A. and RICHARDS, D. Pulmonary insufficiency; study of thirty-nine cases of pulmonary fibrosis. *Medicine*, 28: 1, 1949.
- 6. Austrian, R., McClement, J., Renzetti, A., Donald, K., Riley, R. and Cournand, A. Clinical and physiologic features of some types of pulmonary diseases with impairment of alveolarcapillary diffusion; syndrome of "alveolarcapillary block." Am. J. Med., 11: 667, 1951.
- RENZETTI, A., EASTMAN, G. and AUCHINCLOSS, J. Chronic disseminated histiocytosis X (Schüller-Christian disease) with pulmonary involvement and impairment of alveolarcapillary diffusion Am. J. Med., 22: 834, 1957.
- COURNAND, A. The syndrome of "alveolar-capillary block." Clinical, physiologic, pathologic and therapeutic considerations. Report of Annual Meeting and Proceedings, Royal College of Physicians and Surgeons of Canada, Oct. 3–4, 1952.
- Marks, A., Cugell, D., Cadigan, J. and Gaensler, E. Clinical determination of the diffusion capacity of the lungs. Comparison of methods in normal subjects and patients with the "alveolar-capillary block" syndrome. Am. J. Med., 22: 51, 1957.
- Donald, K., Renzetti, A., Riley, R. and Cournand, A. Analysis of factors affecting concentrations of oxygen and carbon dioxide in gas and blood of lungs: results. J. Appl. Physiol., 4: 497, 1952.
- Löffler, W. Die flüchtigen Lungeninfiltrate mit Eosinophilie. Schweiz. med. Wchnschr., 66: 1069, 1935.
- 12. Jones, A. and Ogle, E. Loeffler's syndrome with skin manifestations. J. Pediat., 36: 505, 1950.
- 13. VELZEBOER, C. Ocular manifestations in Löffler's syndrome. Brit. J. Ophth., 37: 731, 1953

- Leckert, J. Loeffler's syndrome with cardiac involvement. Arch. Int. Med., 98: 510, 1956.
- WIENER, M. and KNIGHTS, E. Löffler's endocarditis parietalis fibroplastica with eosinophilia. Am. Heart J., 53: 157, 1957.
- Ruzic, J., Dorsey, J., Huber, H. and Armstrong, S. Gastric lesion of Loeffler's syndrome; report of a case with inflammatory lesion simulating carcinoma. J. A. M. A., 149: 534, 1952.
- Zuelzer, W. and Apt, L. Disseminated visceral lesions associated with extreme eosinophilia; pathological and clinical observations on syndrome of young children. Am. J. Dis. Child., 78: 153, 1949.
- 18. Bergstrand, H. Morphologic equivalents in polyarthritis rheumatica, periarteritis nodosa, transient eosinophilic infiltration of the lung and other allergic syndromes. J. Path. & Bact., 58: 399, 1946.
- 19 Engfeldt, B. and Zetterstrom, R. Disseminated ecsinophilic collagen disease; a clinical entity related to Löffler's syndromes. Acta med. Scandinav., 153: 337, 1956.
- Rich, A. and Gregory, J. Experimental demonstration that periarteritis nodosa is manifestation of

- hypersensitivity. Bull. John Hopkins Hosp., 72: 65, 1943.
- 21. VON MEYENBURG, H. Die pathologische Anatomie des "fluchtigen Lungeninfiltrates mit Blut-Eosinophilie." Virchows Arch. f. path. Anat., 309: 258, 1942.
- 22. Broch, O. Case of transient pulmonary infiltration with eosinophilia, with fatal issue after treatment by adrenalin for asthma. *Acta med. Scandinav.*, 113: 311, 1943.
- HARKAVY, J. Vascular allergy. J. Allergy, 14: 507, 1943.
- HEAF, P. and PRIME, F. The compliance of the thorax in normal human subjects. Clin. Sc., 15: 319, 1956.
- SINGER, R. and HASTINGS, A. Improved clinical method for estimation of disturbances of acid-base balance of human blood. *Medicine*, 27: 223, 1948.
- Handbook of respiratory data in aviation. National Research Council, Washington, 1944.
- COMROE, J., FORSTER, R., DUBOIS, A., BRISCOE, W. and CARLSEN, E. The Lung. Chicago, 1955. Year Book Publishers, Inc.

Farmer's Lung*

Report of Two Cases in Which Lung Biopsies Were Performed

ROBERT S. TOTTEN, M.D., DAVID H. S. REID, M.D., HARVEY D. DAVIS, M.D. and THOMAS J. MORAN, M.D.

Pittsburgh, Pennsylvania

THE disease known as farmer's lung in this THE disease known as land, and thresher's country and Great Britain, and thresher's lung in Sweden, is a distinct clinical entity that apparently was first described in the medical literature by Campbell in 1932 [1]. Although the etiology is obscure, the relationship of this disease to the inhalation of products from spoiled ("moldy") * hay is well established. The condition is characterized by a sudden onset of shortness of breath within hours of exposure to the moldy hay or other vegetable matter, including silage. Dyspnea is the most striking symptom but fever, chills, cyanosis and varying degrees of weakness may also occur. The course varies from a few days to several weeks in most instances and recovery is usually complete. In addition to this acute phase Fuller [2] has described subacute and chronic forms. Although there are several series reported in the European literature [1-5] we were unable to find any detailed report of this disease originating in this country. Evidently because of the self-limited nature of the disease, the histopathologic changes in the acute or subacute phases have not been described. The purposes of this communication are to report two cases of farmer's lung which occurred in Western Pennsylvania, to describe the histopathology of the lung biopsy specimens, and to discuss certain phases of the pathogenesis.

CASE REPORTS

CASE I. On September 3, 1953, a thirty-four year old farm laborer worked two hours in a silage bin

* Moldy hay is described by farmers as that seen after prolonged rainfall during the period between cutting and stacking or baling. When this hay is worked weeks or months later, clouds of white dust arise from it. The same phenomenon has been observed in wet silage. Fuller [2] states that numerous organisms have been cultured from this material but no group predominates.

removing the moldy surface layer of three-month old corn silage. The dust from the silage arose "like a fog" around him. Three hours later such extreme dyspnea developed that he could "barely speak." He described his respirations as being rapid and shallow, as if he were "only using the uppermost part of his lungs." He had cyanosis, weakness, prostration, violent headache, generalized aches and pains, and slight vomiting, as well as chills and fever (with temperature up to 104°F.), sweating, and a pulse rate of 130 per minute. No cough, expectoration or wheezing occurred. He was admitted to a local hospital on September 6, 1953, and was in an oxygen tent two to three weeks. He improved slowly and was discharged on October 17, 1953. He returned to work two weeks later with no complaints.

A year later he had a similar illness after working with moldy grass silage. He was admitted to a hospital that night with severe dyspnea and continued in severe distress for three weeks before recovering slowly. He returned to work two months after the onset of the acute illness.

In January 1957 he worked for some weeks in a barn which contained bales of moldy hay. During this time he became progressively dyspneic until he had to stop work in late January.

Apart from having had arthritis for six years, he had had no other serious illness.

When admitted to the Presbyterian Hospital on February 12, 1957, he had dyspnea on slight exertion and cyanosis of the lips and fingernail beds. Hiš respiratory rate was 25 per minute. There was no wheezing. The anteroposterior diameter of his chest was increased, but breath sounds were well transmitted. His chest was hyper-resonant. Widespread fine crackling inspiratory rales were heard. Changes consistent with moderate rheumatoid arthritis were present in the fingers, toes, wrists and knees. The remainder of the physical examination revealed nothing of significance.

The hemoglobin was 15.6 gm./100 ml., hematocrit 48 per cent, sedimentation rate 38 mm./hour, and the white blood cell count ranged from 7,100 to 10,600

^{*} From the Departments of Pathology and Medicine, University of Pittsburgh, School of Medicine, Presbyterian Hospital, Woman's Hospital, and Eye and Ear Hospital, Pittsburgh, Pennsylvania.

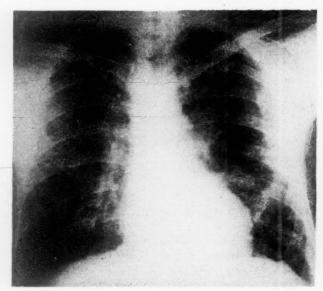


Fig. 1. Case I. Roentgenogram of the chest taken on September 8, 1953, showing bilateral fan-shaped interstitial infiltration of the lungs.

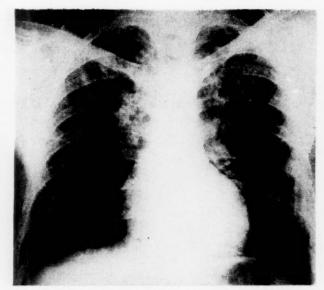


Fig. 2. Case 1. Roentgenogram of the chest taken on October 13, 1953, showing some resolution of the process with right hilar prominence.

per cu. mm. The differential count was 64 per cent neutrophils, 28 per cent lymphocytes, 2 per cent monocytes and 6 per cent eosinophils. The total serum proteins were 6.2 gm./100 ml., albumin 3.1 gm./100 ml., globulin 3.1 gm./100 ml. Routine urinalysis, and blood glucose, blood urea nitrogen and serum uric acid values were within normal limits. Two sputum cultures contained mixed bacteria; Neisseria catarrhalis and beta hemolytic streptococcus predominated. Smears and cultures of sputum for tubercle bacilli were negative. Cultures of sputum, urine and lung tissue for fungi revealed no growth. Skin tests for

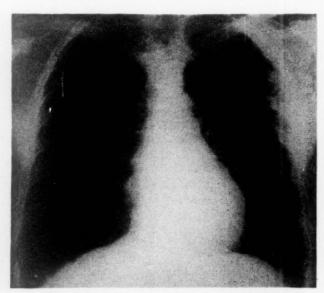


Fig. 3. Case I. Roentgenogram of the chest taken on February 13, 1957, showing slight nodularity of the bronchopulmonary markings.

tuberculosis, histoplasmosis and coccidioidomycosis were negative. The vital capacity was less than 30 per cent of predicted normal, calculated on a basis of surface area. The arterial oxygen saturation was 84 per cent, and after ten minutes of 100 per cent oxygen, 100 per cent. An electrocardiogram showed posterior displacement of the QRS and T vectors in the precordial leads.

Review of the roentgenograms of the chest from the patient's other hospital admission on September 8, 1953, revealed a fan-shaped interstitial infiltration throughout both lungs. (Fig. 1.) A roentgenogram taken on October 13, 1953, showed some resolution of the general process with right hilar enlargement. (Fig. 2.) X-ray examination of the chest at this admission (February 13, 1957) showed slight nodularity of the bronchopulmonary markings consistent with residual fibrosis. (Fig. 3.)

Thoracotomy was performed on February 19, 1957, and a wedge of the lingula of the left lung removed. The surgeon described fibrous pleural adhesions and small nodules palpable beneath the pleura. The patient's postoperative course was uneventful; he improved slowly, and was discharged on February 27, 1957. Administration of prednisone (10 mg., four times a day) was started five days before his discharge and continued at home for a total of four weeks.

The striking microscopic changes in the lung included numerous miliary and submiliary granulomas, extensive interstitial thickening with slight fibrosis, and a focal type of bronchiolitis, occasionally of the obliterating type. The granulomas, often peribronchial, were composed of large pale histiocytes and occasional multinucleated giant cells of the "foreign body" type. (Fig. 4.) Minimal fibrous tissue

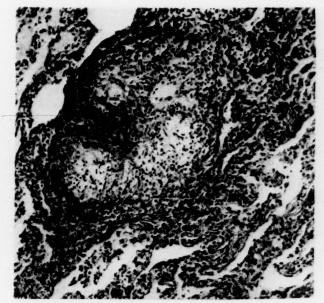


Fig. 4. Case I. Interstitial miliary granuloma composed of histocytes and multinucleated giant cells.

proliferation was noted in a few of the granulomas, but areas of necrosis or calcification were not observed. The interstitial thickening, although considerable, did not involve all portions of the section. In most areas the thickening was caused by infiltration of histiocytes and lymphocytes. In others, there was an increase in fibrous connective tissue. Many foci of atypical bronchiolar regeneration and prominence of the alveolar lining cells were observed along with the interstitial thickening. Many bronchioles were markedly distorted. (Fig. 5.) Some of these were compressed and narrowed by the granulomatous reaction in the surrounding parenchyma. An occasional large bronchiole contained a granulomatous inflammatory reaction in the wall with considerable increase in fibrous tissue and almost complete obliteration of the lumen. (Fig. 6.) Collections of lymphoid tissue, occasionally with germinal follicles, were often conspicuous around involved bronchioles. In some of these areas of lymphocytic hyperplasia the bronchiolar architecture was almost completely destroyed. Less striking changes in the lung included collapse and emphysema, considerable fibrous thickening of the pleura, and patchy collections of histiocytes in the alveolar spaces. The cytoplasm of many of the histiocytes contained fine vacuoles. No foreign material was demonstrated by ordinary light or by polarized light. Acid-fast, periodic-acid-Schiff and Gridley fungus stains were all negative. The patchy interstitial fibrosis and the dense pleural scarring were well demonstrated by a trichrome stain.

CASE II. A thirty-eight year old white man, who had lived on a farm for most of his life, had his first episode of dyspnea in October 1950, a few hours after

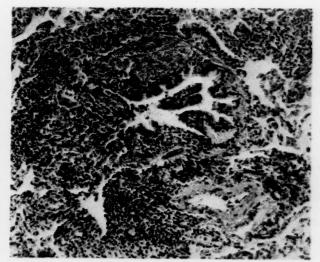


Fig. 5. Case I. Infiltration of lymphocytes, plasma cells and histocytes in bronchiolar wall and surrounding lung.

threshing. He was acutely ill for about a week with dyspnea, chills, fever and a mild cough. One year later, again after threshing, he had a similar illness lasting about the same length of time. Subsequently each winter he had frequent attacks of acute dyspnea and fever, each lasting about a week and associated with the handling of moldy hay. In December 1956 he had an especially severe attack, following which he continued to have chronic incapacitating dyspnea. The shortness of breath continued throughout the winter. He had not experienced wheezing with any of these attacks. He had had no other serious illness.

Examination on admission to Presbyterian Hospital (April 19, 1957) revealed a thin white man with slight cyanosis of the lips and fingernail beds. The antero-

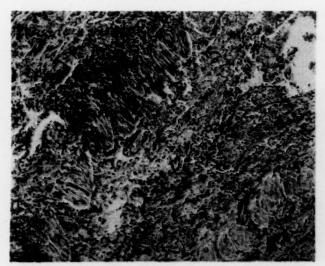


Fig. 6. Case I. Longitudinal section of a bronchiole which is evidenced by smooth muscle bundles extending diagonally across the field. Fibrosis and granulomatous reaction within and around bronchiole.

NOVEMBER, 1958

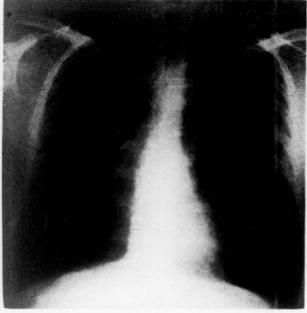


Fig. 7. Case II. Roentgenogram of the chest taken on April 20, 1957, showing signs of emphysema, depressed diaphragms, and prominent pulmonary artery shadows at the hila. The lung fields are unusually clear.

posterior diameter of the chest was increased. His chest was hyper-resonant. Breath sounds were distant with slight prolongation of the expiratory phase. Widespread medium rales were heard. The heart was not enlarged but a right ventricular protodiastolic gallop and accentuated pulmonary second sound were heard. Slight ankle edema was present.

The hemoglobin was 16.2 gm./100 ml., the hematocrit 53 per cent, the sedimentation rate 10 mm. per hour, and the white blood cell count 7,800 per cu. mm. The differential count was 69 per cent neutrophils, 2 per cent band forms, 28 per cent lympho-

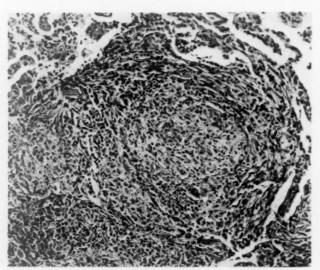


Fig. 9. Case II. Two small miliary granulomas consisting chiefly of histiocytes.

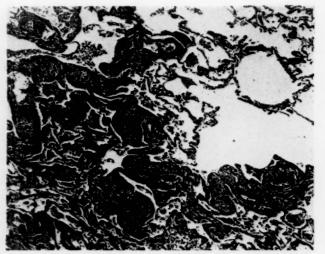


Fig. 8. Case II. Low power photomicrograph of lung showing small emphysematous spaces and prominent granulomatous interstitial inflammation.

cytes and 1 per cent monocytes. Routine urinalysis and blood urea nitrogen and glucose levels were within normal limits. Four sputum cultures showed mixed bacteria; gamma hemolytic streptococcus, and N. catarrhalis predominated. One sputum culture revealed a fungus identified as the saprophyte Mycelia sterila by the Mycology Unit of the Communicable Disease Center in Chamblee, Georgia. Two other sputum cultures for fungi showed no growth. His pulmonary vital capacity was approximately 50 per cent of normal, calculated on a basis of surface area. The arterial oxygen saturation with the patient at rest was 94.7 per cent; after exercise, 92.4 per cent; after ten minutes of 100 pe cent oxygen, 99.2 per cent. The electrocardogram was within normal limits. Roentgenographic examination of the chest showed signs of emphysema with unusually clear lung fields, depressed diaphragms, and prominent pulmonary arterial shadows at the hila. The heart was normal in size and position. (Fig. 7.)

On April 23, 1957, thoracotomy and biopsy of the lingula of the left lung were performed. The surgeon described a normal-appearing lung and pleural cavity. He made an uneventful recovery and improved sufficiently to be discharged on May 4, 1957.

The small wedge of pulmonary tissue obtained at biopsy was covered by a thin pleura and contained one focal area of minimal emphysema surrounded by a reaction which differed only slightly from that sene in the specimen from the first patient. The emphysematous spaces rarely involved more than four to six alveoli. (Fig. 8.) The granulomas were more numerous but often smaller in this specimen than in the first. They were made up of histiocytes, foreign body type giant cells, and occasional strands of fibrous tissue. (Fig. 9.) Many of them clearly lay within the thickened alveolar walls. Giant cell reaction was much more prominent than in the preceding patient. Three

AMERICAN JOURNAL OF MEDICINE

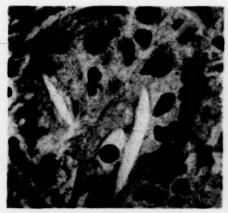


Fig. 10. Case II. Multinucleated giant cell containing two biconvex spaces.

types of foreign material were observed in the giant cells. One consists of biconvex empty spaces 15 to 30 microns long and 3 to 6 microns in thickness. (Fig. 10.) Approximately six of these were seen in twentyfour sections. One oval brownish yellow body with a prominent central condensed rod was seen in one of the periodic acid-Shiff preparations. One piece of a broad filamentous structure 8 microns wide and approximately 30 microns long was seen. (Fig. 11.) It had a thin slightly refractile external covering which was continuous with one transverse band reminiscent of the nodal structure of bamboo. No organisms were identified in the sections stained by the Ziehl-Neelsen and periodic acid-Shiff methods. The interstitial reaction (Fig. 12) was similar to that previously described, but no significant degree of interstitial fibrosis was seen in the trichrome or Verhoeff-van Gieson preparations. The infiltration of histiocytes and lymphocytes in terminal bronchioles was similar. Several small lymphoid follicles were seen.

COMMENTS

Both of these cases fulfill the historical and clinical criteria for the diagnosis of farmer's lung. The principal symptom in each patient was dyspnea accompanied by varying degrees of fever, chills, weakness and cyanosis. Each was related to exposure to moldy hay or silage. Both patients showed dyspnea, cyanosis, and scattered pulmonary rales as well as the physical signs of emphysema. Cough was not a prominent symptom and wheezing was absent. Both improved during hospitalization. Although one patient (Case 1) received prednisone it is not possible to determine whether or not his course was significantly altered by this drug.

Although there are a number of clinical reports of this disease, we were able to find only two instances in which death occurred and

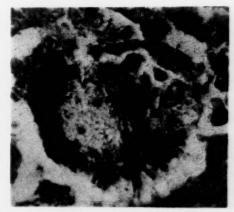


Fig. 11. Case II. Multinucleated giant cell containing broad filamentous structure.

autopsies were performed. One of these patients died of miliary tuberculosis [2]. The other was a forty-seven-year old farmer who died two years after his first admission for dyspnea [3]. Since he did not improve, tuberculosis was also considered clinically. The autopsy revealed marked focal fibrosis and emphysema, but no granulomas or evidence of silica. His terminal event was thought to have been caused by streptococcal pneumonia. From the evidence in the brief histopathologic description and two illustrations, we do not believe that the changes were the same as those in our case.

A similar clinical entity is said to occur in horses exposed to moldy hay. This is described [6,7] as a chronic progressive debilitating disease usually resulting in death ("broken-windedness" or "heaves"). The histopathologic changes described are those of marked emphysema and

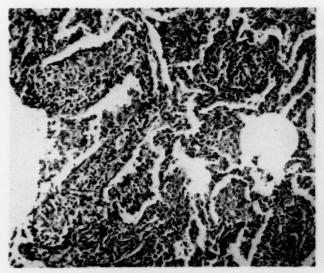


Fig. 12. Case II. Interstitial infiltration of lymphocytes, plasma cells and histocytes.

NOVEMBER, 1958

interstitial fibrosis [6]. These may represent the late manifestations of a condition similar to farmer's lung. We were unable to find any description of the histopathologic changes in the acute or subacute form in horses.

In 1950 Zettergren [8] produced changes in rabbit lungs which were strikingly similar to our two cases by exposing the lungs to sterilized threshing dust. The changes produced were alveolar emphysema and submiliary interstitial histiocytic granulomas. By adding monilia (previously isolated from the dust) to the sterilized threshing dust, the lesions were accentuated and in a few instances caseous necrosis resulted. He concluded that the combination of dust and monilia was probably responsible for the clinical entity of thresher's (farmer's) lung. Monilia has been implicated by other authors in the past [3,4] but proof of this is still lacking. Neither the clinical nor the pathologic picture of farmer's lung resembles known types of moniliasis [9]. Unless more conclusive evidence is found, it seems unlikely that this organism can be considered as the etiologic agent.

Several authors [2,3,5] have suggested that hypersensitivity may be an element in the development of the disease. There is some support for this concept in Zettergren's experiments. Increased serum gamma globulin concentrations were observed in rabbits ten weeks after exposure to dust and monilia. His experiments were not designed to test this thesis, however, since none of the animals were exposed to subsequent doses of dust or monilia. The results of skin tests using antigens prepared from hay and several species of fungi have been inconclusive [2]. Hypersensitivity may be an important factor in the development of farmer's lung, but definite evidence of this is lacking.

Silo-filler's disease also occurs in farm workers, but it has sufficient clinical and histopathological differences to be separated readily from farmer's lung. Inhalation of nitrogen dioxide or other oxides of nitrogen has been established as the cause of silo-filler's dsease [10,11].

Although a relationship of farmer's lung to the inhalation of moldy hay products is evident, the ultimate cause is not known. However, on the basis of these two specimens, certain comments concerning pathogenesis may be made. The differences between the two cases appear to be quantitative, in that the patient in Case I shows more interstitial and pleural fibrosis as well as a more severe obliterating bronchiolitis. These

histologic observations are confirmed by the roentgenograms which show persistent fibrosis in this patient. The essential histologic features of the disease are a granulomatous inflammation of the lung involving alveolar walls and bronchioles. If the disease is severe and/or prolonged sufficiently, this granulomatous reaction may result in interstitial fibrosis and obliterating bronchiolitis. These lesions are thought to be responsible for the development of emphysema.

SUMMARY

Two cases of farmer's lung are reported, with a discussion of the histopathologic changes seen in lung biopsy specimens.

Farmer's lung is a distinct clinical entity characterized by severe dyspnea and varying degrees of fever, chills, cyanosis and prostration. It is closely related to the inhalation of moldy hay or silage although the ultimate etiologic agent is not known. The occurrence of two cases in Western Pennsylvania suggests that the disease is probably more common in this country than is indicated in the literature. The essential histologic features are granulomatous pneumonitis and bronchiolitis, varying degrees of interstitial fibrosis, focal obliterating bronchiolitis and emphysema.

Acknowledgment: We are indebted to Dr. Frank J. Gregg who permitted use of the records of these patients.

ADDENDUM

Since the submission of this article for publication two additional papers [12,13] on farmer's lung have been published by authors from this country.

REFERENCES

- CAMPBELL, J. M. Acute symptoms following work with hay. Brit. M. J., 2: 1143-1144, 1932.
- 2. Fuller, C. J. Farmer's lung: a review of present knowledge. *Thorax*, 8: 59-64, 1953.
- FAWCITT, R. Fungoid conditions of the lung—Part 1. Brit. J. Radiol., 9: 172–186, 1936.
- FAWCITT, R. Occupational diseases of the lungs in agricultural workers. *Brit. J. Radiol.*, 11: 378–392, 1938.
- Törnell, E. Thresher's lung. Acta med. Scandinav., 125: 191–219, 1946.
- COHRS, P. Lehrbuch der speziellen pathologischen Anatomie der Haustiere, pp. 117–119. Jena, 1952. Fischer.
- UDALL, D. H. The Practice of Veterinary Medicine, 4th ed., pp. 32-35. Menasha, 1943. George Bante Publishing Co.

AMERICAN JOURNAL OF MEDICINE

- 8. ZETTERGREN, L. Thresher's lung (pulmonary moniliasis): experimental investigation. *Upsala läk. forh.*, 55: 257-313, 1950.
- 9. Conant, N. F., Smith, D. T., Baker, R. D., Cal-Laway, J. L. and Martin, D. S. Manual of Clinical Mycology, 2nd ed., pp. 175–180. Philadelphia, 1954. W. B. Saunders Company. 10. Delaney, L. T., Schmidt, H. W. and Stroebell,
- DELANEY, L. T., SCHMIDT, H. W. and STROEBEL,
 C. F. Silo-filler's disease. Proc. Staff Meet., Mayo Clin., 31: 189-198, 1956.
- Lowry, T. and Schuman, L. M. "Silo-filler's disease"—a syndrome caused by nitrogen dioxide.

 J. A. M. A., 162: 153–160, 1956.
- J. A. M. A., 162: 153-160, 1956.
 12. Frank, R. C. Farmer's lung—a form of pneumoconiosis due to organic dusts. Am. J. Roentgenol., 79: 189-215, 1958.
- DICKIE, H. A. and RANKIN, J. Farmer's lung: an acute granulomatous interstitial pneumonitis occurring in agricultural workers. J. A. M. A., 167: 1069–1076, 1958.

Chiari's Network*

LLOYD S. RALSTON, M.D. and WALTER A. WASDAHL, M.D.

Grand Forks, North Dakota

CHIARI'S network is a relatively rare finding in the adult heart estimated to occur in 1.5 to about 3 per cent of autopsy examinations [1,2]. This interesting anomaly consists of a lacework of fine or coarse fibers originating about the margins of the eustachian and thebesian valves and attaching in the area of the crista terminalis or floor of the right atrium. The meshwork represents vestigial remains of the right valvulae venosae and septum spurium when resorptive and incorporative processes of development have failed to mold normally the structures into the walls of the right atrium.

Embryology. Normally the original single atrial cavity is divided into two chambers, the right and left atria, in the following manner [3]: An outgrowth of tissue arises from the mid-dorsal wall of the atrium and fuses with the endocardial cushions near the junctions of the atrial and ventricular cavities—this is the septum primum. Subsequently another crescentic outpouching of tissue appears just inferior and to the right of the septum primum, called the septum secundum. This latter septum incorporates the left valve of the sinus venosus and, together with the septum primum, eventually accomplishes the division of the original single atrium into the two adult chambers—the right and left atrium. (Fig. 1.)

The sinus venosus is composed of a right and left horn and right and left valve flaps. The right horn is incorporated into the right atrium and in doing so gives rise to the superior and inferior vena caval entrances into the atrial chamber. The right valve, at one time so prominent as nearly to divide the right atrial chamber, gradually regresses. The cephalic portion finally is seen as the crista terminalis in the adult heart. The caudal portion of the right venous valve is split by the inferior sinus septum into the eustachian (valve of inferior vena cava) and thebesian (valve of the coronary sinus) valves. The aforementioned inferior sinus septum represents the remains of the left horn of the sinus venosus

which has been incorporated into the posterior wall of the right atrium and migrates in the process of development. The left horn of the sinus venosus (left duct of Cuvier) thus is in position to persist as part of the coronary sinus. The septum spurium represents merely the point of fusion of the upper limits of the right and left venous valves on the dorsal and cephalic wall of the right atrium. (Fig. 2.)

In this process of embryological development by which the various openings, valves and crests of the adult heart are formed, resorptive processes take place. When this normal resorptive process is left incomplete in the structures of the right valvulae venosae and its continuation, the septum spurium, the final anomaly is known as Chiari's network.

CASE REPORT

This sixty-seven year old man was first seen on January 29, 1957, with the complaint of frontal headache which had its onset in the preceding week. There was the additional complaint of inability to find the right word to express himself. During the past week he had experienced increasing unsteadiness of gait and a generalized weakness to such an extent that he felt virtually unable to get around. No other complaints were elicited.

The past history, pieced together from relatives and one previous hospitalization elsewhere, revealed that the patient had evidently suffered from fairly severe hypertension for about ten years and had had several episodes of paroxysmal tachycardia. In September 1953 he had what appeared to be a rather extensive occlusion of vessels supplying the left cerebral hemisphere with resulting right hemiparesis and aphasia. The hemiplegia had gradually regressed over many months until fair function returned to the involved extremities. However, marked lability of emotions and episodes of confusion had developed, and there was no improvement in the aphasia. His emotional lability had led to rather frequent changes in medical attendants.

Physical examination revealed an elderly male who had marked expressive aphasia. The gait was

^{*} From the Departments of Medicine and Pathology of the University of North Dakota School of Medicine and the Department of Internal Medicine, Grand Forks Clinic, Grand Forks, North Dakota.

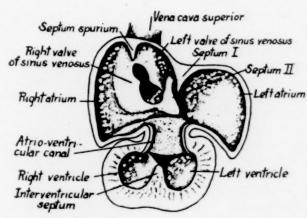


Fig. 1. Inner view of dorsal wall of heart of a human embryo 10 mm. in size. From: YATER, W. M. Am. Heart J., 1935; JORDAN, H. E. and KINDRED, J. E. Textbook of Embryology. New York, 1926. D. Appleton & Co.

ataxic, but it seemed more due to weakness than true ataxia. Strength and movement was remarkably good in all extremities, and no residual neurological findings were present. The blood pressure was 170/110 mm. Hg, the pulse was regular at a rate of 90. The ocular fundi showed marked arteriolar tortuosity and arteriovenous bridging, while about the periphery of the discs were seen numerous small hemorrhages. The heart was enlarged to percussion, the point of maximal impulse being 14 cm. to the left of the midclavicular line. No murmurs were heard. The peripheral arteries felt firm and hardened.

X-ray film of the chest showed a heart of aortic configuration with a cardiothoracic ratio of 16:29. The aorta was dilated and tortuous. The lung fields were clear. The hemoglobin was 16.3 gm. per cent, the white blood cell count was 5,450 per cu. mm. The urinalysis was negative.

The patient was seen on several occasions with no marked change until May 6, 1957, at which time he was admitted to the emergency room of the Deaconess Hospital. One hour previously, while sitting in a local hotel, a sudden severe frontal headache developed, vision became blurred and speech slurred. This was followed shortly by nausea and profuse vomiting.

Physical examination revealed a patient exhibiting obtunded sensorium, slurred speech, and inability to see clearly. The blood pressure was 230/130 mm. Hg and the pulse 100 with regular rhythm. The pupils were round, regular, equal, and reacted to light. The ocular fundi were unchanged. The heart now presented a basal systolic murmur which was harsh and loud. The only neurological finding of importance was a questionable extensor Babinski sign on the left. The X-ray film of the chest was unchanged, and a flat film of the abdomen showed normal findings. The white blood cell count was 11,700 per cu. mm. with a normal differential count, hemoglobin 16.6 gm. per cent. The urinalysis was negative. The blood urea

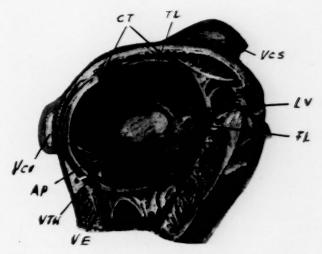


Fig. 2. Right atrium with the lateral wall removed to show the relationship of the orifices of the atrium and the usual forms of the eustachian and thebesian valves. V.E., eustachian valve; V.Th., thebesian valve; A.P., auricula posterior; V.c.i., inferior vena cava; C.t., crista terminalis; T.L., tuberculum loweri; V.c.s., superior vena cava; L.V., limbus Vieussenii; F.L., foramen Lannelongeus. From: YATER, W. M. Am. Heart J., 1936; TANDLER, J. In: Bardeleben: Handbuch der Anatomie des Herzens. Jena, 1913. Gustav Fischer.

nitrogen was 17 mg. per cent. A serological test for syphilis was negative.

During the succeeding few hours the patient became comatose, incontinent at both sphincters, and quietly died.

At autopsy the characteristic changes of longstanding hypertensive cardiovascular renal disease were noted consisting of myocardial hypertrophy of the left ventricular type, granular kidneys, multiple foci of anemic encephalomalacia in the left temporal and parietal cortex, and terminal extensive intracerebellar hemorrhage with rupture into the fourth ventricle. The configuration of the heart was that of left ventricular hypertrophy. Upon opening the right atrium a network of coarse to fine fibers covering the orifice of the inferior vena cava was noted. Attached to the central portion of this net was a long, coiled embolus, 20 cm. in length, with several areas of constriction and branching, giving in general the appearance of a cast of the iliofemoral vein. This embolus extended in a tortuous manner into the right ventricle. The network in which the embolus was entangled had its superior attachments at the upper margin of the vena cava extending medially to attach to the crista terminalis in the region of the orifice of the superior vena cava. Inferiorly it was attached to the wall of the atrium in the region below and adjacent to the coronary sinus. The strands of the network were seen to vary from very thin and lacy fibers to relatively coarse ones having a diameter up to 1.5 cm. At their attachments, the network fibers expanded into membranous valve-like widenings. Examination of



Fig. 3. Embolus, 20 cm. in length, is shown firmly entangled in the fibers of Chiari's right auricular network.

the pulmonary arteries revealed two fragments of embolic material in the main branches of the pulmonary artery without attachment and without evidence of peripheral embolization or infarction. Examination of the veins of the extremities revealed extensive phlebothrombosis of the right popliteal space. The iliofemoral vein was free of embolus except for small loosely attached fragments of thrombus material in the region of the valve.

COMMENTS

It has been suggested that the congenital right auricular network of Chiari may have clinical as well as pathological importance. The following implications have been mentioned as associated with this anomaly: (1) production of cardiac murmur, (2) production of precordial thrill, (3) focus for initiation of thrombus, (4) net in which peripheral emboli are trapped in the heart, (5) possible association with auricular rhythm disturbances, and (6) interference with circulation and aeration of blood contributing to circulatory failure of other etiology.

Production of Cardiac Murmur. Alvarez and Hermann [4] in 1931 reported a case in which the clinical findings of aortic regurgitation were present. Additionally, a low pitched musical diastolic murmur was heard in the right parasternal region at the level of the third rib downward along the sternal border. This murmur blended into a distant systolic purr. The authors also likened the murmur to the venous hum heard at times over the jugular bulb. At autopsy a Chiari network was found, and it was proposed that this peculiar auscultatory phenomenon might be due to the anomaly. Several years later Wilson [5] observed a patient presenting a

murmur almost identical with that described by Alvarez and Hermann. Again the murmur was compared to the venous hum and was likewise reminiscent of the Roger's murmur associated with interventricular septal defect. Necropsy demonstrated the right auricular network. In our case a murmur was not heard until the final admission. This may well represent an auscultatory finding having its origin in obstruction to the flow of blood into the right atrium caused by the large embolus suspended in the network.

Production of Precordial Thrill. In the case reported by Alvarez [4] a thrill was felt at the right base, which was diastolic primarily but continued into systole.

Focus for Initiation of Thrombus [6]. The threads of this process churning about in the right atrium readily suggest a favorable nidus for clot formation [7]. This is probably especially true, as Yater [8] suggests, when the circulation is slow or conditions become favorable for clotting. Chiari's [6] first case demonstrated the reticulum to be the site for initiation of thrombus formation and eventual fatal embolization. Wilson [5], Alvarez [4] and Jordan [7] also suggest that the network is found in a site favorable to the formation of thrombi which may later break off and embolize. Yater [8] refers to nine instances in which thrombi were present in the network and mentions two of his own.

Net in which Peripheral Emboli are Trapped in the Heart. Haas [9] reported one case in which an embolus entered the right auricle through the inferior vena cava and became trapped in the network. The site of origin was the femoral vein. The suggestion was made that a possible fatal pulmonary embolization had been prevented. Yater [8] reports a second case in which an embolus, 11.5 cm. in size, from a large peripheral vein became trapped in Chiari's net. The origin of this embolus was believed to be the right iliac or femoral vein. The currently reported case is evidently the third in which a potentially fatal pulmonary embolization from a peripheral source was prevented by Chiari's network. (Fig. 3.)

Possible Association with Auricular Rhythm Disturbances. Because of the anatomical relationship of the network to the right auricular part of the conduction system it has been suggested that some association with rhythm disturbances is possible [7]. Disease of the network might further add to the possibility of aberrant rhythm. This has not been proved but is interesting from a

AMERICAN JOURNAL OF MEDICINE

speculative viewpoint. Of the eight patients reported on by Helwig [1] two had auricular fibrillation and one had both a gallop rhythm and right bundle branch block. Jordan's [7] two patients each had auricular fibrillation, but it was believed that an adequate explanation for the rhythm disturbance was present without indicting the "network." In Yater's [2] fourth case the patient had auricular flutter, and the pathology suggests a possible focus for circus movement. The distribution of cardiac muscle was such that a continuous ring of possible conducting tissue was ranged about the mouth of the inferior vena cava. The patient dealt with in this report had a history of several episodes of what was evidently paroxysmal rapid heart action. The relationship of this to Chiari's network would be purely conjectural.

Interference with Circulation and Aeration of Blood Contributing to Circulatory Failure of Other Etiology. Lesieur and Froment [10] indicated that in their patients disturbances in circulation and aeration of blood had been present. In the case of Alvarez and Hermann [4] the authors suggested that the position of the network suspended between the orifices of the superior and inferior vena cava possibly played some part in obstructing venous return to the heart. This, coupled with the aortic disease, contributed to an extreme degree of circulatory failure.

SUMMARY

1. A case of Chiari's network is presented. In this case potentially fatal embolization of the lung was prevented by the embolus becoming lodged in the fibers of the net.

2. The suggested clinical implications of this anomaly, both as applied to the presently reported case and to those in the literature, are reviewed.

REFERENCES

- 1. Helwig, F. C. The frequency of anomalous reticula in the right atrium of the human heart "Chiari network." Am. J. Path., 8: 73, 1932.
- YATER, W. M. Variations and anomalies of the venous valves of the right atrium of the human heart. Arch. Path., 7: 418, 1929.
- PATTEN, B. M. Human Embryology, 2nd ed., pp. 656–673. New York, 1953. Plakiston Co.
- ALVAREZ, J. and HERMANN, G. Unusual signs from an expansive Chiari network along with signs of a syphilitic aortic regurgitation. Am. J. Syph., 15: 532, 1931.
- Wilson, R. A case of Chiari's network associated with a murmur resembling the bruit de Roger. J. A. M. A., 111: 917, 1938.
- CHIARI, H. Concerning reticular formations in the right auricle of the heart. Beitr. z. path. anat. u. z. Allg. Path., 22: 1, 1897.
- JORDAN, W. R. Two cases of Chiari's network. Arch. Path., 2: 840, 1926.
- YATER, W. M. The paradox of Chiari's network. Am. Heart J., 11: 542, 1936.
- Haas, W. Über einen weiteren Fall von Netzbilderungen in rechten Vorhofe mit einem in demselben verfangenen Embolus. Inaug. Diss. Karlsruhe, 1916. Cited by Helwig [7].
- Lesieur, C., Froment, J. and Cremieu, R. Coexistence of an interauricular communication and an anomaly of the valve of Thebesius. Lyon med., 116: 1047, 1911.
- 11. Huepher, W. and Berghoff, R. S. Two hearts with Chiari network. Tr. Chicago Path. Soc., 13: 78, 1929.

Pseudoaortic Stenosis Produced by Ventricular Hypertrophy*

Bernard A. Bercu, M.D., Gerald A. Diettert, M.D., † William H. Danforth, M.D., Ernest E. Pund, Jr., M.D., ‡ Robert C. Ahlvin, M.D. § and Robert R. Belliveau, M.D.

St. Louis, Missouri

THE clinical diagnosis of aortic stenosis usually is not difficult. Recently, direct pressure readings from the left ventricular cavity have made it possible to establish the diagnosis in atypical cases and to determine the magnitude of the systolic pressure gradient across the aortic valve [1,2]. However, Brock has reported three cases of hypertrophy of the left ventricular outflow tract, which he believes may be secondary to systemic hypertension, in which a systolic gradient was found between the left ventricular cavity and the aorta [3]. It is the purpose of this report to present the clinical and postmortem findings of an unusual case of myocardial hypertrophy which also simulated aortic stenosis. The clinical course of a brother of the patient, who may have a similar condition, is also presented.

CASE REPORTS

CASE I. P. D., a male truckdriver thirty-five years of age, was admitted to the Barnes Hospital for the first time in March 1956 for investigation of a cardiac murmur. As a child he had had frequent sore throats but denied symptoms of acute rheumatic fever. In 1940 he had been rejected by the Army because of a cardiac murmur. For five years prior to admission he had noted slight dyspnea on exertion. He denied chest pain, orthopnea, paroxysmal dyspnea, syncope, cyanosis and edema. His father died at age fifty-four of "asthma and pneumonia" and his mother at age fifty-five of "heart disease" of unknown type. One brother (Case II) had undergone an aortic valvulotomy at the Barnes Hospital in April 1955 for aortic stenosis. A third brother, age thirty-two, had recently been examined at a Naval hospital and had been found to have an "enlarged heart." A fourth brother, a sister, two half brothers and a half sister, all born of the patient's mother, were living and well.

The patient was well developed and nourished, of

sthenic habitus, and did not appear ill. His blood pressure was 130/52 mm. Hg and his pulse rate 92 per minute. The physical examination was entirely within normal limits with the exception of the heart. It was enlarged; a forceful apical beat was felt in the sixth intercostal space in the anterior axillary line. A systolic thrill was palpable at the apex and along the left sternal border as high as the third intercostal space. A loud, harsh systolic murmur was heard over the entire precordium but was loudest along the left sternal border and at the apex. Aortic and pulmonic second sounds were of equal intensity.

The hemogram, urinalysis, cardiolipin test, stool analysis, non-protein nitrogen, fasting blood sugar and antistreptolysin 0 titer were all within normal limits or negative. Electrocardiogram and chest roentgenograms (Fig. 1) were interpreted as typical of left ventricular enlargement.

A direct left ventricular puncture using the transthoracic approach was performed. A systolic pressure of 260 mm. Hg was recorded. (Fig. 2.) Simultaneously, the brachial systolic pressure was 130 mm. Hg. This systolic gradient was considered diagnostic of aortic stenosis in spite of the atypical position of the cardiac murmur and thrill.

The patient was discharged from the hospital and followed up in the outpatient department. Because of gradual increase in dyspnea on exertion he was readmitted to the Barnes Hospital on September 30, 1957. The results of the physical examination were essentially the same as recorded previously. An electrocardiogram again revealed left ventricular enlargement. It was decided that the patient would benefit from aortic valvulotomy. On October 15, a bilateral anterior thoracotomy was performed under hypothermia. The aorta was not dilated and only a faint thrill was palpable in the region of its valve. Following occlusion of venous inflow the aorta was opened just distal to the aortic valve. The valve cusps were found to be pliable and normal in appearance. Exploration of the cavity of the left ventricle revealed it to be too

^{*} From the Cardiopulmonary Laboratory, Department of Medicine, and Department of Pathology, Washington University School of Medicine, and the Barnes Hospital, St. Louis, Missouri.

[†] St. Louis Heart Association Fellow in Cardiopulmonary Research, 1956–1958. Present address: Missoula, Montana. ‡ National Foundation for Infantile Paralysis Fellow in Cardiopulmonary Research, 1957–1958. Present address: Denver, Colorado.

[§] Life Insurance Medical Research Fund Fellow, 1957–1958.

small to admit the surgeon's finger. The aorta was closed and the occluding tapes on the venae cavae released. Several attempts to obtain a measurement of the left ventricular pressure by needle puncture were unsuccessful as the chamber could not be entered. Ventricular fibrillation occurred twice but responded promptly to electric shock. The chest was closed and the patient was warmed without further incident. During the early postoperative period he became agitated, hypotensive, and his respiratory exchange was poor. He died ten hours after operation.

At postmortem examination the major pathologic lesions were limited to the heart which was symmetrically hypertrophied and weighed 770 gm. Its epicardial surface was covered with a thin fibrinous exudate of recent development but fibrous adhesions or other stigmas indicating diseases of a more chronic nature were absent.

Multiple transverse sections of the heart revealed that both ventricular walls were markedly thickened, the right measuring 7 mm. and the left 16 mm. Most remarkable was the reduction of both ventricular cavities to mere uniform slits throughout their entire length including the apices. (Figs. 3 and 4.) The aortic, pulmonary and tricuspid valves were completely normal. The mitral valve was also normal except for a slight degree of uniform thickening throughout both cusps. The chordae tendinae were normal but for slight thickening and they were of usual length. The endocardium was smooth and glistening throughout. It was of normal thickness except for a single patch, 2 by 3 cm., on the interventricular septum along the left ventricular outflow tract. In this area it was 1 mm. thick but no ridge was

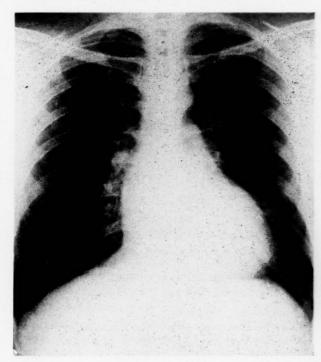


Fig. 1. Chest roentgenogram in Case I, typical of left ventricular enlargement seen commonly in aortic stenosis.

The myocardium was normal with the exception of several small areas of gray scar in the interventricular septum and left ventricle. Even the largest of these sparsely scattered scars was less than 2 mm. in its greatest diameter. An irregular area of congestion, 2 by 2 by 3 cm., was found in the myocardium of the

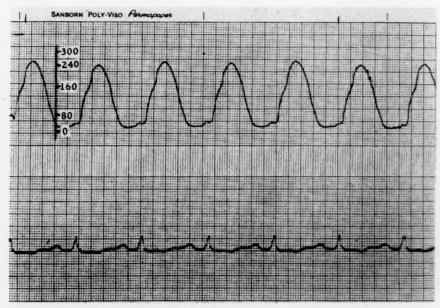


Fig. 2. Left ventricular pressure tracing obtained in Case I. Simultaneous peripheral systolic pressure was 130 mm. Hg.

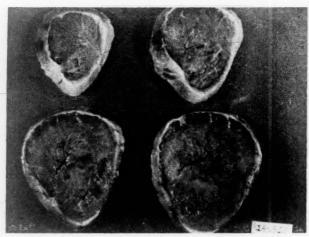


Fig. 3. Transverse sections of the heart in Case 1. Note the reduction of the ventricular cavities to mere slits by the markedly hypertrophied myocardium.

interventricular septum. (Fig. 4.) The coronary arteries were normal in their distribution (Schlesinger type II), and were focally narrowed by arteriosclerotic placques which reduced the lumens to about half of normal. Occlusions were absent.

In multiple microsections of the heart stained with hematoxylin and eosin, or with phosphotungstic acid-hematoxylin, were found only the focal scars seen grossly, and many hypertrophied muscle fibers with typical large nuclei. (Fig. 5.) Neither degenerative changes nor inflammatory infiltrate were present. Preparations to demonstrate amyloid and abnormal amounts of fat or glycogen were negative.

On both gross and microscopic examination other viscera were congested, including the lungs, liver, spleen and kidneys. Renal vascular lesions indicative of hypertension were absent. The small pulmonary arteries were slightly affected by fibrous intimal thickening consistent with the patient's age. Two organizing thrombi were found in small branches of the pulmonary artery.

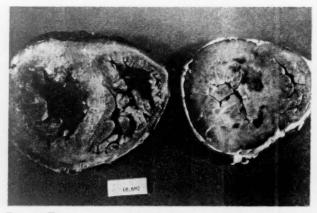


Fig. 4. Transverse section of the heart in Case I (right) compared with a similar section from a hypertrophied heart (900 gm.) in a case of calcific aortic stenosis.

Case II. L. D., a white policeman thirty-four years of age, brother of P. D. (Case I), was first seen at the Barnes Hospital in April 1953. He denied symptoms of acute rheumatic fever in the past. In February 1951 he had been admitted to another hospital for painless hematemesis and had been treated with six blood transfusions. An extensive investigation had failed to reveal a cause for the bleeding but he had been told for the first time that he had a cardiac murmur. Since then he had noted increasing dyspnea on exertion. He complained of occasional dull precordial pains which lasted several minutes and were not related to exertion. He had observed infrequent palpitations.

The patient, like his brother, was well developed and nourished, sthenic in habitus, and did not appear ill. His blood pressure was 100/60 mm. Hg and his pulse rate 86 per minute. The physical examination was entirely within normal limits except for the heart. His heart was not clinically enlarged, but its apical beat was forceful and localized. A systolic thrill was palpable at the apex and along the left sternal border. A loud, harsh systolic murmur was present in the same area as the thrill. The aortic second sound was diminished in intensity.

The hemogram, urinalysis and cardiolipin test were within normal limits or negative. An antistreptolysin 0 titer was 400 units. Electrocardiogram and roentgenograms of the chest revealed left ventricular enlargement. The patient was treated with digitalis and discharged with a diagnosis of mitral insufficiency due to rheumatic heart disease.

He was not seen again until March 1955 when he returned to the Barnes Hospital because of continued dyspnea on exertion. Physical examination showed the same changes as those noted in 1953 except that the intensity of the aortic second sound was now louder than the pulmonic second sound.

Roentgenograms of the chest revealed left ventricular enlargement and minimal left auricular enlarge-

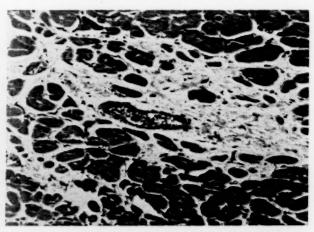


Fig. 5. One of the scattered areas of fibrosis in the myocardium. There are no degenerative changes in the hypertrophied muscle fibers. Hematoxylin and eosin.

AMERICAN JOURNAL OF MEDICINE

ment. An electrocardiogram was again interpreted as left ventricular enlargement. Catheterization of the left side of the heart was performed utilizing the transthoracic approach. The configuration of the tracing obtained in the left auricle was normal and there was no diastolic pressure gradient across the mitral valve. Pressure within the left ventricle was 280/0 mm. Hg while a simultaneous determination of the brachial artery pressure was 120/80 mm. Hg. These findings were considered to be the result of aortic valvular stenosis in spite of the somewhat atypical clinical findings.

On April 8, 1955, the patient underwent aortic valvulotomy using a blind transventricular approach with a Bailey dilator. He tolerated the procedure well. The surgeon believed that the valve fractured easily. Postoperative pressures for determination of the left ventricular-aortic gradient were not obtained. No question was raised about the existence of aortic valvular stenosis at the time of the operative procedure.

During the first ten months after operation the patient noted a gradual increase in exercise tolerance and has since been essentially asymptomatic. He has noted occasional transient vague precordial pain not related to exertion. There has been no change in the findings on physical examination during the post-operative period, and his blood pressure has always been within normal limits.

COMMENTS

The cause of the ventricular hypertrophy in Case I is not evident. Neither a significant degree of coronary arterial disease nor fibroelastosis, both of which may lead to myocardial hypertrophy, was present at autopsy. Clinical evidence is lacking for an endocrinopathy such as acromegaly or giantism in which growth hormone is thought to contribute to myocardial hypertrophy.

This case would appear not to be an example of "idiopathic myocardial hypertrophy" [4–6]. Outstanding clinical features of idiopathic hypertrophy, namely marked cardiomegaly, intractable cardiac failure and pulmonary embolization, were not present. Significant murmurs are generally lacking while cardiac arrhythmias are a common feature. Prominent ventricular dilatation is found in all cases. Mural thrombi and a significant degree of endocardial fibrosis are commonly present. Necrosis and fibrosis of the myocardium are often observed histologically.

The patient described in Case II probably has an abnormality similar to that of his brother. Preoperative findings suggesting aortic stenosis were identical in both cases and the operative

approach to the valve in Case II was blind. The third brother who was recently found to have an "enlarged heart" may have a similar condition. A type of familial cardiomegaly resembling "idiopathic myocardial hypertrophy" has been described by several observers [7-9]. Vacuolization of muscle and conducting fibers, dense patchy interstitial fibrosis and minimal infiltration of the myocardium with lymphocytes and monocytes are characteristic of this condition. Although the cases described in this report may represent familial cardiomegaly, the severe myocardial hypertrophy without dilatation and the paucity of degenerative changes in the myocardium suggest that Case I differs from those previously described.

The classic doctrine that myocardial hypertrophy occurs with increased resistance to blood flow cannot be applied in this instance since evidence was lacking to suggest either valvular obstruction or systemic hypertension. In addition, dilatation of the cardiac chambers which usually accompanies hypertrophy when due to increased myocardial work was absent. It would be extremely unlikely that obstruction of both the pulmonary and systemic circulations could have been present to explain the severe but equal degrees of hypertrophy of the two ventricles. Because of these considerations, and because of the strong evidence for a familial occurrence of this curious ventricular hypertrophy, it must be concluded that the process originated as a primary myocardial hypertrophy of both ventricles.

The hemodynamic process resulting in a systolic pressure gradient between the left ventricular cavity and aorta in Case I may be similar to that suggested by Brock, namely a secondary obstruction due to hypertrophy of the outflow tract [3]. A similar phenomenon has been observed by others in right ventricular hypertrophy [10,11]. However, in our case not only the outflow tract but the entire cavities of both ventricles were strikingly reduced in a uniform manner.

SUMMARY

The clinical and postmortem findings in a case of unexplained ventricular hypertrophy which simulated aortic stenosis is reported. Left ventricular puncture revealed a systolic pressure gradient of 130 mm. Hg between the left ventricle and aorta. At postmortem examination marked myocardial hypertrophy without chamber dilatation and a normal aortic valve were

found. Reduction of the cavities of both ventricles by hypertrophied myocardium was striking, and may have been responsible for the finding of a pressure gradient at catheterization of the left side of the heart. The patient's brother, who has similar clinical and catheterization findings, may represent another example of this curious type of ventricular hypertrophy.

818

REFERENCES

- LAWRENCE, G. H., ZIMMERMAN, H. B., BERCU, B. A. and BURFORD, T. H. Evaluation of mitral and aortic valvular disease by left heart catheterization. Surg., Gynec. & Obst., 101: 558, 1955.
- BROCK, R. C., MILSTEIN, B. B. and Ross, D. N. Percutaneous left ventricular puncture in the assessment of aortic stenosis. *Thorax*, 11: 163, 1956.
- Brock, R. C. Functional obstruction of the left ventricle. Guy's Hosp. Rep., 106: 221, 1957.
- Serbin, R. A. and Chojnacki, B. Idiopathic cardiac hypertrophy. New England J. Med., 252: 10, 1955.

- Elster, S. K., Horn, H. and Tuchman, L. R. Cardiac hypertrophy and insufficiency of unknown etiology. Am. J. Med., 18: 900, 1955.
- Levy, R. L. and Von Glahn, W. C. Cardiac hypertrophy of unknown cause. Am. Heart J., 28: 714, 1944
- 7. Evans, W. Familial cardiomegaly. *Brit. Heart J.*, 11: 68, 1949.
- 8. Gaunt, R. T. and Lecutier, M. A. Familial cardiomegaly. *Brit. Heart J.*, 18: 251, 1956.
- CAMPBELL, M. and TURNER-WARWICK, M. Two more families with cardiomegaly. *Brit. Heart J.*, 18: 393, 1956.
- Engle, M. A., Holswade, G. R., Goldberg, H. P. and Glenn, F. Regression after open valvulotomy of infundibular stenosis accompanying severe valvular pulmonic stenosis. *Circulation*, 16: 876, 1957.
- BLOUNT, S. G., JR., VAN ELK, J., BALCHUM, O. J. and SWAN, H. Valvular pulmonary stenosis with intact ventricular septum; clinical and physiologic response to open valvulotomy. *Circulation*, 15: 814, 1957.

Metamucil[®] does BOTH!

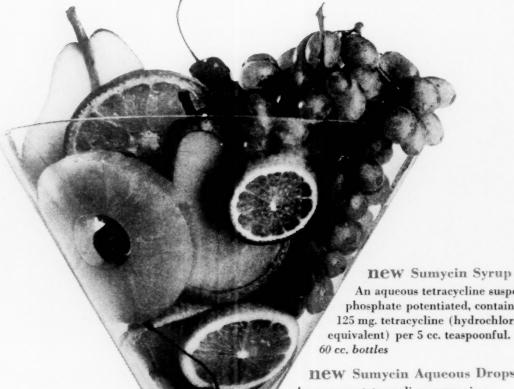
In constipation, Metamucil produces SOFT, easy stools and activates gentle peristalsis. By adsorbing and retaining water within the stool Metamucil prevents hard feces from forming. And it adds to intestinal residue a soft, plastic bulk which ACTIVATES the normal reflex activity of peristalsis.

Metamucil is a brand of psyllium hydrophilic mucilloid with dextrose.

SEARLE

the flavor of fruit and a broad spectrum antibiotic

syrup/aqueous drops



... delicious aqueous suspensions to assure patient acceptance for effective tetracycline therapy ... children especially will like their tasty fruit flavor

An aqueous tetracycline suspension, phosphate potentiated, containing 125 mg. tetracycline (hydrochloride

equivalent) per 5 cc. teaspoonful.

new Sumyein Aqueous Drops

An aqueous tetracycline suspension, phosphate potentiated, containing 100 mg. tetracycline (hydrochloride equivalent) per cc.

10 cc. bottles with the new, unbreakable 'FLEXIDOSE' DROPPER

Also available:	Tetracycline phosphate complex equiv. to tetracycline HCl (mg.)						
Sumycin Capsules	250 mg. per capsule	Bottles of 16 and 100					
Sumycin Half Strength Capsules	125 mg. per capsule	Bottles of 16 and 100					
Sumyein Intramuscular with Xylocaine*	250 mg. per vial	1 dose vials					
Sumyein Intramuscular with Xylocaine*	100 mg. per vial	1 dose vials					



Squibb Quality - the Priceless Ingredient



Arrest the anxiety factor in heart disease

without affecting autonomic function

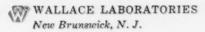
"A cardiac breakdown might be forestalled or arrested" by effective treatment of nervous tension and anxiety.* Adjunctive therapy with meprobamate "definitely reduced nervous tension and anxiety" in all heart patients (80 cases), and enhanced recovery from acute cardiac episodes in many cases.*

*Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957. Because of its unexcelled safety, Miltown is well suited for tranquilization of chronic heart patients. It is well tolerated, relatively nontoxic, and produces no blood dyscrasias, liver impairment, parkinsonism, or nasal stuffiness.

It does not mask toxicity of other drugs.

Miltown

Miltown is the original meprobamate, discovered and introduced by



IS THIS YOUR PATIENT?

1.



EARLY POSTMENOPAUSE

Complains of low back pain, vague aches and fatigue Posture is poor No x-ray evidence of bone lesions 2.



LATER POSTMENOPAUSE

Back pain is severe, spreading to hips ("girdle pain") Patient is round shouldered, walks with a stoop X-ray reveals compression fractures of lower vertebrae 3.



70 AND OVER

Fracture of hip after a minor fall X-ray reveals fracture of neck of femur X-ray reveals compression fractures of lower lumbar vertebrae

These three patients have osteoporosis. Early diagnosis and treatment with "Formatrix" is important because osteoporosis is probably the only age change that can be averted. With "Formatrix" therapy, relief from the symptoms of *low back pain, vague aches* and *fatigue* may be obtained in as little as a few weeks. "Formatrix" supplies the essential materials to stimulate increased bone formation and prevent further loss of bone substance that leads eventually to loss of height, stooped posture, and disabling fractures.

The highest incidence of osteoporosis may be found among the 14,000,000 women in the U.S.A. who are 55 years of age and over. Some investigators claim that almost all women past the menopause will show some degree of osteoporosis; furthermore, if all these women were examined carefully, 50 per cent would show x-ray evidence of decreased bone mass.

Suspicion may be the handiest diagnostic tool since presenting symptoms vary from mild to severe and incapacitating pain, and no x-ray evidence of spinal degeneration is available until about 30 per cent of the bone matrix is lost. Between these two extremes there are other signs of estrogen deficiency such as wrinkled and thinning skin, a tendency to appear older than stated years; there may also be hypercalciuria when postmenopausal osteoporosis is complicated by acute osteoporosis of disuse.

Osteoporosis is primarily an atrophic condition of bone matrix formation and any factor that depresses osteo-blastic activity or retards the formation of protein and connective tissue such as *prolonged immobilization*, *cortisone therapy*, or *malnutrition* will favor development of osteoporosis in both male and female.





"FORMATRIX" contains three most essential bone building materials necessary for matrix formation, estrogen, androgen and vitamin C.

The estrogen component of "Formatrix" stimulates osteoblastic activity, thus aiding calcium and phosphorus deposition; it also imparts a feeling of "wellbeing." The anabolic action of methyltestosterone promotes the synthesis of protein and restores a positive

nitrogen balance. Together, these hormones have a greater effect on bone and protein metabolism than either alone, and side effects are minimized because of the opposing action of the two steroids on sex-linked tissues. Vitamin C plays an important role in formation of intercellular cement substance and amino acid synthesis. "Formatrix" has a large amount of vitamin C to aid in new bone matrix formation and to further help in the healing of fractures.

"FORMATRIX" - each tablet contains:

Conjugated estrogens equine ("Premarin" 6)									
Methyltestosterone	10.0	mg.							
Ascorbic acid	400.0	mg.							
Dosage: I tablet a day - In the female, three weeks of treatment with a rest period of one week between									

courses is recommended.

Supplied: Tablets, bottles of 60 and 500.

LITERATURE AVAILABLE ON REQUEST

1.



EARLY POSTMENOPAUSENo x-ray evidence of bone lesion

2



LATER POSTMENOPAUSE X-ray reveals compression fracture of lower vertebrae

3.



70 AND OVER
X-ray reveals fracture of neck of femur

TO RELIEVE LOW BACK PAIN - TO PROMOTE HEALING OF FRACTURES

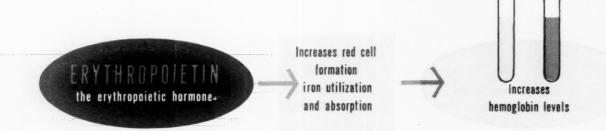
in osteoporosis

FORMATRIX"

for matrix formation

ENHANCE ERYTHROPOIETIN FORMATION TO EFFECTIVELY TREAT THE COMMON ANEMIAS

RONGOVITE-mf



Erythropoietin, the erythropoietic hormone, is the newly recognized physiologic regulator of red cell formation.

Outstanding investigators have proved cobalt to be the only known therapeutic agent which stimulates erythropoietin formation. Acting through this natural physiologic channel, erythropoietin produced by cobalt increases red cell formation. In consequence, iron utilization and absorption and hemoglobin synthesis are accelerated. Thus, more efficient utilization of administered iron makes possible greatly reduced iron dosage and better tolerated therapy in the new cobalt-iron hematinic—RONCOVITE-MF.

PRACTICAL APPLICATIONS—Extensive clinical experience has repeatedly demonstrated that a combination of cobalt and iron (Roncovite-MF) is superior to iron alone in the common hypochromic anemias, such as menstrual anemia, anemia of pregnancy, nutritional anemia of infancy, and anemia due to gastrointestinal bleeding.^{2,3,4,5}

Roncovite-MF may even reverse the erythropoietic failure seen in refractory anemia of chronic infection or inflammation.^{6, 7}

Formula: Each enteric coated, green tablet contains:

Cobalt chloride (Cobalt as Co..3.7).... 15 mg. Ferrous Sulfate, exsiccated........ 100 mg.

Maximum adult dose:

One tablet after each meal and at bedtime.

Supplied: Bottles of 100 tablets.

Complete bibliography on request.

LLOYD BROTHERS, INC. CINCINNATI 3, OHIO

IT'S LOVE AT FIRST TASTE

liquid vitamin supplement

Because children love the delicious orange flavor of PALADAC, there's very little chance they will forget vitamin time, even if Mother does.

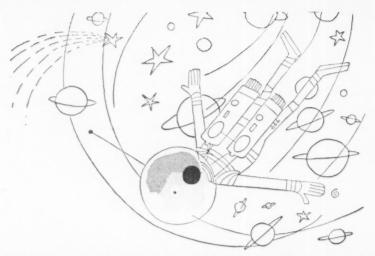
Since PALADAC contains a balanced formula of nine important vitamins, what more reliable and pleasant way to help assure proper vitamin intake for growing youngsters? PALADAC is even-flowing, readily miscible with milk, truit juice, or other foods if desired, and requires no refrigeration.

supplied: 4-onice and 16-onice bottles.

PARKE, DAVIS & COMPANY DETROIT 32, MICHIGAN







BRING HIM BACK FROM OUTER SPACE

ILIIPAN

to feed the inner man



With REDISOL (vitamin B_{12})—new zest for meals. Soluble REDISOL tablets (25, 50, 100, 250 mcg.) and cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) mix readily with liquids.

REDISOL is a trade-mark of Merck & Co., Inc.



MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

Psoriasis can destroy the most beautiful body in the world ...

LIPA N capsules added

to your armamentarium will provide ...

maximum effect with minimum inconvenience to the patient. No messy ointments or lotions. When following your prescribed regimen an impressive percentage of patients will become free of the symptoms.

LIPANIZE THE PSORIATIC

TO OBTAIN SYMPTOM-FREE PATIENTS

Complete LIPANIZATION of the patient is essential for successful clinical results. LIPANIZATION is accomplished with saturation doses of LIPAN and produces a gradual reduction of the hypercholesteremia and hyperlipemia usually present in the psoriatic.

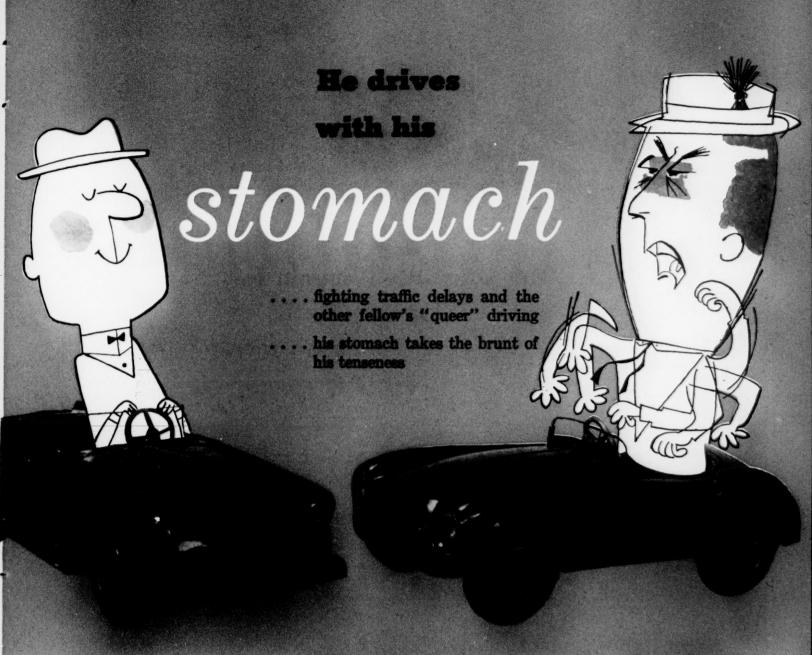
Dosage: Initial administration of LIPAN requires twelve (12) to fifteen (15) capsules daily in conjunction with food intake. After complete LIPANIZATION which requires about ten days, dosage is then adjusted to the quantity of food ingested.

Maintenance Dosage: After complete remission of lesions the dose is usually one (1) to two (2) capsules with each intake of food.

LIPAN Capsules or Tablets contain: Specially prepared highly activated, desiccated and defatted whole Pancreas. Thiamin HCl. 1.5 mg. Viramin D. 500 LU.

Available: Bottles 180's, 500's

Samples Literature upon request Spirt & Co., Inc. Waterbury, Conn.



BUTIBEL® antispasmodic · sedative

quiets "nervous," spastic stomachs—with the efficient sedation of BUTISOL SODIUM® butabarbital sodium 10 mg. and the antispasmodic effect of *natural* extract of belladonna 15 mg. (per tablet or 5 cc.)

BUTIBEL TABLETS / ELIXIR, PRESTABS® BUTIBEL R-A

(Repeat Action Tablets)



MCNEIL LABORATORIES, INC.

Philadelphia 32, Pa



"This substance [Vitamin K₁] has added greatly to the safety of anticoagulant therapy"

reverse anticoagulant-induced hypoprothrombinemia

MEPHYTON_®

VITAMIN K1

the only available preparation chemically identical with naturally-occurring vitamin K_1 ... "has a more prompt, more potent and more prolonged effect than the vitamin K analogues"

Dosage: Orally, to modify anticoagulant effects: 5 to 10 mg. initially; 15 to 25 mg. for more vigorous action. Intravenously, for anticoagulant-induced bleeding emergencies, 10 to 50 mg.; may be repeated as indicated by prothrombin time response. (Some clinicians advise their patients to keep a supply of tablets on hand at all times; if gross bleeding occurs, the patients are instructed to take 10 mg. and phone the doctor.1)

Supplied: Tablets, 5 mg., bottles of 100. Emulsion, each 1-cc. ampul contains 50 mg., boxes of 6 ampuls.

Other indications: To normalize prothrombin time-before surgery, in obstructive jaundice, hepatic disease, impaired gastrointestinal absorption, deficiency of vitamin K in the newborn, and following the administration of antibiotics, sulfonamides, and salicylates. 'Mephyton' is a valuable addition to the physician's bag for emergency use.



MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

Mephyton is a trade-mark of MERCK & CO., INC.

- 1. Wright, I. S.: Early use of anticoagulants in treatment of myocardial infarction, J.A.M.A. 163: 918-921, March 16, 1957.
- 2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.

The ultimate today in therapy for menopausal disorders, menstrual disorders, inoperable breast cancer, male climacteric.

Ultandren A new oral androgen tablet with 5 times the potency of methyltestosterone tablets.

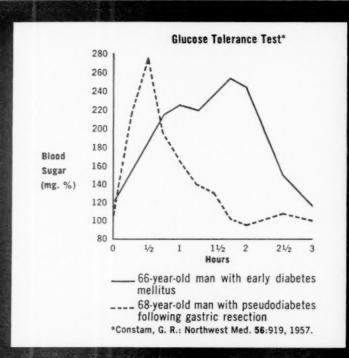
Ultandren presents a new range of possibilities for simple, convenient treatment in conditions stemming from certain types of hormonal imbalance.

Small oral doses provide full androgenic effects, previously obtainable only with parenteral testosterone preparations.

Easy tablet administration eliminates the painful injections, local reactions and skipped doses attending the use of intramuscular testosterone, as well as the foreboding aspects of treatment-room therapy.

Begin now to prescribe Ultandren, truly the ultimate today in therapy for menopausal disorders, menstrual dysfunction and premenstrual tension, male climacteric, and palliation of inoperable

AN
AMES
CLINIQUICKT.M
CLINIQUICKT.M
CLINICAL BRIEFS



besides diabetes, what diseases may cause symptoms of polyuria, polydipsia, increased fatigability and loss of weight?

Various renal diseases with isosthenuria, portal obstruction, functional dipsomania, hyperparathyroidism, acromegaly, primary aldosteronism, chronic mercury poisoning, hypervitaminoses A or D, Hand-Schüller-Christian lipoidosis, fructosuria, pentosuria and sucrosuria.*

COLOR-CALIBRATED CLINITEST® Reagent Tablets

the STANDARDIZED urine-sugar test for reliable quantitative estimations

- · full color calibration, clear-cut color changes
- · established "plus" system covers entire critical range
- · standard blue-to-orange spectrum long familiar to diabetics
- · unvarying, laboratory-controlled color scale



AMES COMPANY, INC • ELKHART, INDIANA Ames Company of Canada, Ltd., Toronto

46858



NEW THERAPY...TO DEFEAT THE MIGRAINE PARADOX* 'MIGRAL'®

- · relieves headache
- · dispels visual disturbances
- and · overcomes nausea and vomiting

*The paradox of migraine — increased nausea due to ergotamine administration — may now be successfully combated with 'Migral'. The recognized benefits of ergotamine and caffeine in 'Migral' are favorably enhanced by the addition of cyclizine hydrochloride, a specific to overcome nausea.

Dosage: 2 to 3 tablets at first warning of an attack, then 1 or 2 tablets every half hour; not more than 6 tablets should be taken for any single attack.

Supplied: 'Migral' tablets, containing ergotamine tartrate 1 mg., 'Marezine'® brand Cyclizine Hydrochloride 25 mg., and caffeine 50 mg.



BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York



to accelerate convalescence...

Sustagen®

Complete food, Mead Johnson powder

Builds tissue, promotes wellbeing, enhances rehabilitation

Specific treatment may vary infinitely in details, but one factor remains constant—the urgent need of every seriously ill patient for therapeutic nutrition.

With Sustagen you can give your patients extra nutritional reserves which they need to withstand both medical and surgical crises and debilitating diseases.

Sustagen in itself is a balanced diet and can be given by mouth or by tube. It can be used alone or as a supplement to the diet, for short term or prolonged nutritional therapy. Sustagen supplies every known essential nutrient for maintenance or rehabilitation.

Detailed information on the use of Sustagen in many clinical conditions is provided in the booklet "Nutritional Therapy: The Use of Food in the Management of Illness and Injury." Your Mead Johnson Representative will gladly supply you with a copy...or you may write to us, Evansville 21, Indiana.







NOW...

FOR ADULTS - CHILDREN - INFANTS

A CONTRAST MEDIUM THAT
FULFILLS ALL THE
CRITERIA FOR
RADIOLOGIC EXAMINATION
OF THE
ALIMENTARY CANAL

- * a true solution-permits delineation of gastric and duodenal mucosa, and identification of small ulcers
- does not inspissate-risk of residual hard masses eliminated; safe for use in the acutely ill and in cases of suspected or known obstruction
- ** minimal absorption passes readily along alimentary tract with negligible absorption
- virtually nontoxic—safe on accidental, or deliberate, introduction into body cavities; may be used in post-anastomosis studies
- miscible with blood-allows detection of bleeding points and visualization of bleeding ulcers
- low viscosity-permits demonstration of small fistulous connections, including tracheoesophageal fistulae in infants
- cathartic effect-eliminates delay in surgical procedures, or in serial or follow-up radiologic studies
- well tolerated-side reactions minimal; contraindicated only in individuals with iodine sensitivity
- may be administered orally, by tube, or by rectum

Gastrografin, providing 76% sodium and methylglucamine diacetylaminotriiodobenzoates, is supplied in bottles of 120 cc. (4 fl. oz.).

SQUIBB

New York 22, N. Y.



Squibb Quality — The Priceless Ingredient

SCASSBOORAPING IS A SQUIRE TRADEMARK

The American Journal of Medicine

TEN YEAR INDEX

July 1946 through June 1956.

·····ORDER FORM······

The American Journal of Medicine, Inc. 11 East 36th Street, New York 16, N. Y.

Please send me the new Ten Year Index to The American Journal of Medicine for which I enclose \$5.00 U.S.A.—\$5.50 Foreign

Name.																

City......Zone....State....

(New York City residents, add 3% sales tax)



This subject and author index provides an invaluable aid for quick reference and review purposes to the articles and authors who have appeared in the journal during the past ten years.

RAD GIA



THE WM. S. MERRELL COMPANY
New York - CINCINNATI - St. Thomas, Ontario

WITH THE FIRST DAY'S DOSE

you'll see renewed vitality—even before you notice the "tonic" effect of ALERTONIC vitamin-mineral supplementation.

REPRINT ORDER FORM

THE AMERICAN JOURNAL OF MEDICINE 11 East 36th Street, New York 16, N. Y.

Please send me the following Seminars reprinted from The American Journal of Medicine:

☐ BLOOD COAGULATION	\$2.00	
☐ HEMOLYTIC ANEMIAS	\$2.00	
☐ CARBOHYDRATE METABOLISM	\$2.00	
☐ Allergy	\$2.00	
☐ DISEASES OF THE PANCREAS	\$2.00	
☐ BONE DISEASES	\$2.00	
☐ ATHEROSCLEROSIS	\$2.00	
☐ LIVER DISEASE	\$2.00	
Enclosed is my check		
Name————		
Address —	-	
City	State	

E C M I C

... BRIGHTEN THE OUTLOOK

ALERTONIC alerts the listless, blue patient, brightens his outlook fast, contains a safe, effective psychic energizer.*

... NOURISH THE BODY

Supplementary B-vitamins and minerals give a needed lift to poor appetite and metabolism.

*Meratran-Merrell's subtle-acting, safe alerting agent

Prescription only. One tablespoon t.i.d. Professional literature and samples on request. Write Dept. AT

IRON THERAPY...WELL TOLERATED ...EVEN ON AN EMPTY STOMACH!

excellent results

11,000 CASES**

ferronord

(brand of ferroalusine sulfate complex)

- serum response in 3 hours
- clinical response in days
- between-meal administration for better utilization
- WITH SIDE EFFECTS INSIGNIFICANT¹⁻⁸

48 patients1 - serum iron rose rapidly, Hb. response prompt

given on empty stomach in all cases-no gastric upset, diarrhea or constipation were found

91 patients²—significant reticulocyte response in 6 days on 2 tabs. t.i.d. in moderate hypochromic anemia-found extremely useful even in those with peptic ulcer, gastritis, lack of side effects was reported as quite impressive -slight gastric upset in one patient

102 patients'-a remarkably sharp rise in hemoglobin levels was demonstrated

one complaint of mild constipation

62 patients - reported to be a real advance in iron therapy

2 instances of G.I. upset disappeared with dosage adjustment

563 patients - found to be efficiently absorbed and to provide predictable clinical results

only eight cases of mild intoleranceno side effects even in patients with peptic ulcer

120 patients - peak reticulocyte response on fifth day

not a single complaint of upset, FERRONORD taken on empty stomach in all cases

41 patients' — average daily Hb. rise of 1.6%

well tolerated in peptic ulcer and gastritis patients—given on empty stomach in all cases

10,016 patients* - Hb. response excellent, average treatment period 4-6 weeks

only 4.39% of cases reported any side effectsusually adjusted with dosage

DOSAGE SCHEDULE



Average adult dose: initially, 2 tabs. b.i.d.; severe cases, 2 tabs. t.i.d.

Maintenance dose, 1-2 tabs daily. Each FERRONORD tablet supplies 40 mg. of ferrous iron.



FERRONORD Liquid, 60 cc. dropper bottles, 40 mg. iron per cc.

BIBLIOGRAPHY:

1. Dwyer, T. A.; Clin. Med. 4:457, 1957. 2. Pomeranze, J., and Gadek, R. J.; New England J. Med. 257:73, 1957. 3. Clancy, J. B.; Aldrich, R. H.; Rummel, W., and Candon, B. H.; Am. Pract. & Digest Treat, 8:1948, 1957. 4. O'Brien, T. E.; Onorato, R. R.; Dwyer, T. A., and Candon, B. H.; West. J. Surg. 65:29, 1957. 5. Frohman, I. P., and others: Scientific Exhibit, Sixth Congress Internat. Soc. Hemat., Boston, Mass., Aug. 26-Sept. 1, 1956. 6. Wagner, H.: Landarzt 31:496, 1955. 7. Jorgensen, G.: Arztl. Wchnschr. 10:82, 1955. 8. Aldrich, R. H.; Pomeranze, J.; Clancy, J. B., and others: Scientific Exhibit, A.M.A. Meeting, June, 1957. New York, N. Y.

FERRONDROD (BRAND OF FERROSLYCINE SULFATE COMPLEX) PAT. PENDING



Nordson Pharmaceutical Laboratories, Inc., Irvington, New Jersey

DOCTORS PARKING ONLY

7AM-7PM



ACHROMYCIN®V

Tetraeveline and Citric Acid Lederle

A Decision of Physicians

When it comes to prescribing broad-spectrum antibiotics, physicians today most frequently specify Achromycin V.

The reason for this decided preference is simple.

For more than four years now, you and your colleagues have had many opportunities to observe and confirm the clinical efficacy of Achromycin tetracycline and, more recently, Achromycin V tetracycline and citric acid.

In patient after patient, in diseases caused by many invading organisms, Achromycin achieves prompt control of the infection—and with few significant side effects.

The next time your diagnosis calls for rapid antibiotic action, rely on Achromycin V—the choice of physicians in every field and specialty.



LEDERLE LABORATORIES

a Division of AMERICAN CYANAMID COMPANY Pearl River, New York

Investigator

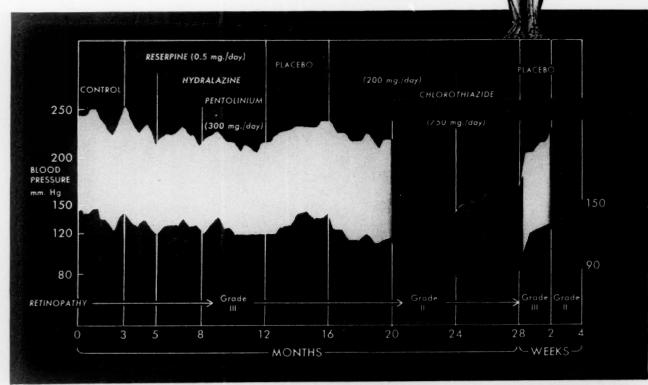
after investigator reports

Wilkins, R. W.: New England J. Med. 257:1026, Nov. 21, 1957.

"Chlorothiazide <u>added</u> to other antihypertensive drugs reduced the blood pressure in 19 of 23 hypertensive patients." "All of 11 hypertension subjects in whom splanchnicectomy had been performed had a striking blood pressure response to oral administration of chlorothiazide." "... it is not hypotensive in normotensive patients with congestive heart failure, in whom it is markedly diuretic; it is hypotensive in both compensated and decompensated hypertensive patients (in the former without congestive heart failure, it is not markedly diuretic, whereas in the latter in congestive heart failure, it is markedly diuretic)...."

Freis, E. D., Wanko, A., Wilson, I. H. and Parrish, A. E.: J.A.M.A. 166:137, Jan. 11, 1958.

"Chlorothiazide (maintenance dose, 0.5 Gm. twice daily) added to the regimen of 73 ambulatory hypertensive patients who were receiving other antihypertensive drugs as well caused an additional reduction [16%] of blood pressure." "The advantages of chlorothiazide were (1) significant antihypertensive effect in a high percentage of patients, particularly when combined with other agents, (2) absence of significant side effects or toxicity in the dosages used, (3) absence of tolerance (at least thus far), and (4) effectiveness with simple 'rule of thumb' oral dosage schedules."



In "Chlorothiazide: A New Type of Drug for the Treatment of Arterial Hypertension,"

[Hollander, W. and Wilkins, R. W.: Boston Med. Quart. 8: 1, September, 1957.

MERCK SHARP & DOHME Division of MERCK & CO., INC., Philadelphia 1, Pa. MS



the effectiveness of DIURILE (CHLOROTHIAZIDE)

in

Hypertension

as simple as 1-2-3

- INITIATE THERAPY WITH 'DIURIL'. 'DIURIL' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day.
- ADJUST DOSAGE OF OTHER AGENTS. The dosage of other antihypertensive medication (reserpine, veratrum, hydralazine, etc.) is adjusted as indicated by patient response. If the patient is established on a ganglionic blocking agent (e.g., 'INVERSINE') this should be continued, but the total daily dose should be immediately reduced by as much as 25 to 50 per cent. This will reduce the serious side effects often observed with ganglionic blockade.
- ADJUST DOSAGE OF ALL MEDICATION. The patient must be frequently observed and careful adjustment of all agents should be made to determine optimal maintenance dosage.

SUPPLIED: 250 mg. and 500 mg. scored tablets 'DIURIL' (chlorothiazide); bottles of 100 and 1,000. 'DIURIL' is a trade-mark of Merck & Co., Inc.

Smooth, more trouble-free management of hypertension with 'DIURIL'

stop penicillin reactions <u>before</u> they become serious

NEUTRAPEN

(NEUTRAlizes PENicillin)

(Penicillinase Injectable,* SchenLabs

the only specific for penicillin reactions

"... if every patient with a penicillin reaction were given penicillinase [Neutrapen] within 24 to 48 hours... I do not think we would see the severe, prolonged reactions we are seeing now."

R. M. Becker, Antibiotics Annual 1957-58.1

Unlike the antihistamines, ACTH or steroids which treat effects, NEUTRAPEN, an enzyme, aborts penicillin reactions by counteracting their cause—it destroys the penicillin itself and is effective in about 97 per cent of cases.² Over 80 per cent of patients obtain clearing of the reaction with one injection.³



Obscure sources—even cases with no history of penicillin therapy respond to NEUTRAPEN when the reaction has been caused by penicillin from such sources as milk, Roquefort or bleu cheese, or penicillin containing vaccines.³

NEUTRAPEN - 800,000 units I.M.—should be given as soon as symptoms appear. May be repeated on the third day if response is not satisfactory. In anaphylactic reactions, after routine emergency measures - 800,000 units intravenously, followed immediately by 800,000 units intramuscularly. contraindications: None. side effects: Occasionally transient local soreness, erythema, and edema; rarely, transitory chills and fever.

supplied: 800,000-unit single-dose vials of lyophilized penicillinase powder. Stable at room temperature in the dry state.

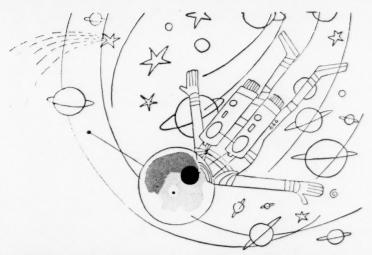
references: (1) Becker, R. M., in Welch, H., and Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 310. (2) Zimmerman, M. C.: Clin. Med. 5:305, 1958. (3) Zimmerman, M. C.: J.A.M.A. 167:1807, 1958.

T. M. REG. U.S. PAT. OFF. *PATENTS PENDING.

55658



SCHENLABS PHARMACEUTICALS, INC . NEW YORK 1, N.Y.



BRING HIM BACK FROM OUTER SPACE

to feed the inner man



With REDISOL (vitamin B_{12})—new zest for meals. Soluble REDISOL tablets (25, 50, 100, 250 mcg.) and cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) mix readily with liquids.

REDISOL is a trade-mark of Merck & Co., Inc.



FEWER ANGINAL ATTACKS.
PROTECTS AGAINST PAIN
AND CONTROLS ANXIETY.
(EQUANIL AND PETN)

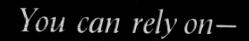
EQUANITRATE*

Meprobamate and Pentaerythritol Tetranitrate

*Trademark



1 அந்த ஆணி அச்ஸ்ட் அன்றன்றனர்கள் (2000 எஸ்.) நார் pentuerythritol tetranitrate (10 mg.)



PROTAMIDE®

represents a significant decrease in the represents a significant decrease in the period of disability for the patient. No specific per multiple vitamin preparations have proved as period of disability for the patient. No specific or multiple vitamin preparations have proved as beneficial as the use of [Protamide]." NEURITIS

MEDICAL CLINICS OF NORTH AMERICA

HERPES ZOSTER

"Protamide is a valuable remedy in the treatment of herpes zoster. It is helpful in relief of pain and apparently aids in involution of the cutaneous lesions.

> Frank C. Combes, et. al. NEW YORK STATE JOURNAL OF MEDICINE

RADICULITIS rener for the type of cases of neuritis which had proved intractable to Vitarelief for the type of cases of neu-.. Protamide provided fast rius winch had proved intractable to vita-min B₁, B₁₂ and physical therapy...it is - Henry W. Lehrer, et. al. now our therapy of choice... NORTHWEST MEDICINE

HERPES OPHTHALMICUS "...it is certain we have obtained more satisfactory results with Protamide than with those drugs previously employed such as the neurovaccines, antibiotics, vitamins, ACTH and corti-ITALIAN JOURNAL OF OPHTHALMOLOGY

HERPES ZOSTER

.Protamide is of definite value in the relief of pain in herpes zoster. Further, vesicles and crusts disappear much more rapidly than in untreated cases."

- William C. Marsh U. S. ARMED FORCES MEDICAL JOURNAL

"Protamide is deemed a safe drug...with the ability to control 80.7 per cent of patients with radiculitis of posterior roots believed due to virus infaction."

- Richard T. Smith NEW YORK MEDICINE

This patient's blood-pressure controlled for the first time without side effects

Remember this particular patient. He typifies the thousands of patients involved in a clinical investigation which promises to bring about a major change in rauwolfia therapy. The patient is being treated in a Massachusetts hospital. His blood pressure without treatment ranged up to 220/138; now for the first time, it is being maintained near normal without side effects. This dramatic case history is part of the story of a remarkable new antihypertensive agent **Singuscept**

coming as soon as sufficient supplies are available... from CIBA, world leader in hypertension research.



three-way mechanism of action



in one molecule

A long step forward

MUREL

Brand of Valethamate bromide

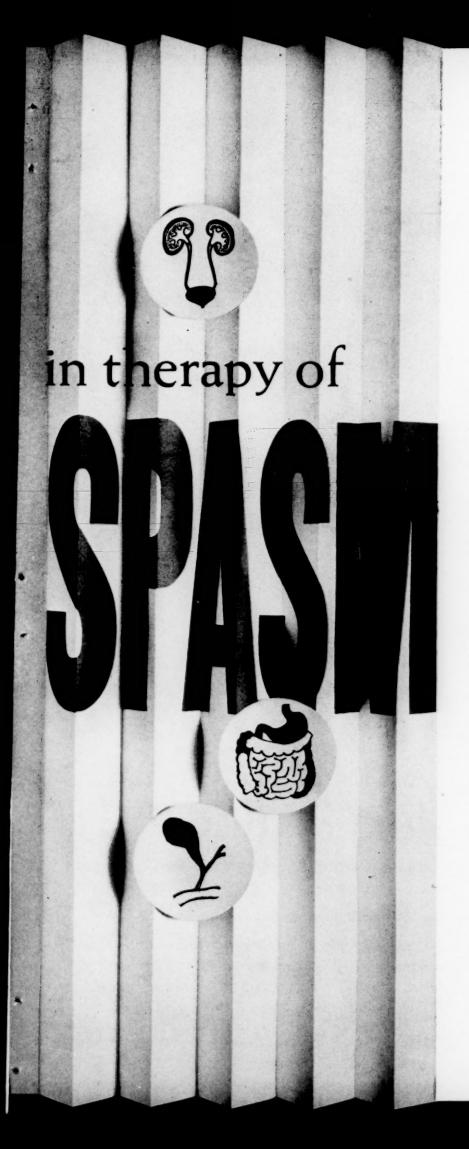
"MUREL" is the newest development of research in quaternary ammonium compounds. It advances today's therapy of G.U., G.I. and biliary tract spasm toward the ideal in decisive relief without intolerance or drug-induced complications. "MUREL" also supplements peptic ulcer therapy by breaking the chain reaction of spasm-pain.

Dosage: Mild to moderate cases: initially, 1 or 2 tablets four times daily. Acute or severe cases: 1 to 2 cc. (10-20 mg.) intravenously or intramuscularly every four to six hours up to maximum of 60 mg. in 24 hour period. The higher dosage range is usually required in spasm of G.U. and biliary tract.

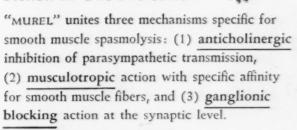
Supplied: "MUREL" Tablets—10 mg. Valethamate bromide, bottles of 100 and 1,000. "MUREL" Injectable—10 mg. per cc., vials of 5 cc. (Also available: "MUREL" with Phenobarbital Tablets—10 mg. Valethamate bromide with ¼ gr. phenobarbital per tablet, bottles of 100 and 1,000.)

Ayerst Laboratories . New York 16, N. Y. . Montreal, Canada









Precludes or Minimizes Untoward Side Effects

"MUREL" is especially well tolerated because:
(1) coordination of the three component actions permits significantly low dosages and also reduces reaction potential of any one mechanism,
(2) a natural specificity confines the anticholinergic action to the effector cells of smooth muscle,
(3) definite but transient ganglionic blocking action eliminates undesirable parasympathetic disturbances, (4) rapid detoxification and excretion prevent cumulative effect.

Widely Useful— Clinically Demonstrated

"MUREL" extends the clinical scope of dependable spasmolytic therapy, with indications ranging from mild to severe hypertonicity. In postoperative genitourinary spasm, cystitis and pyelitis—effective relief of pain and spasm was noted in all of 75 patients. In peptic ulcer—complete or substantial relief from the pain/spasm cycle was reported in 119 out of 127 patients. In biliary spasm and chronic cholecystopathies with or without stones—prompt, complete control of spasm was obtained in 20 out of 22 patients.

Peiser² states that even extremely strong convulsive abdominal pain and violent vomiting could be eliminated or substantially improved, and no unpleasant side effects or toxic reactions were noted at any time.

- 1. Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955.
- 2. Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955.
- 3. Winter, H.: Medizinische, p. 1206 (Aug. 27) 1955.

prompt, aggressive antibiotic action a reliable defense against monilial complications both are often needed when bacterial infection occurs

for a direct strike at infection Mysteclin-V contains tetracycline phosphate complex

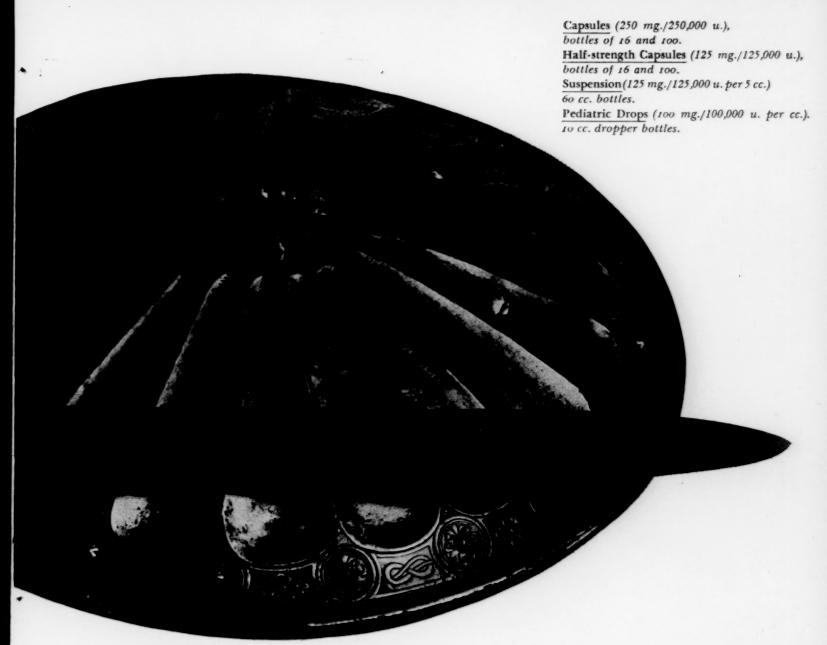
It provides a direct strike at all tetracycline-susceptible organisms (most pathogenic bacteria, certain rickettsias, certain large viruses, and Endamoeba histolytica).

It provides the new chemical form of the world's most widely prescribed broad spectrum antibiotic.

It provides unsurpassed initial blood levels—higher and faster than older forms of tetracycline—for the most rapid transport of the antibiotic to the site of infection.

"MYSTECLIN'®, "SUMYCIN'® AND "MYCOSTATIN'® ARE SQUIBB TRADEMARKS





for protection against monilial complications Mysteclin-V contains Mycostatin

It provides the antifungal antibiotic, first tested and clinically confirmed by Squibb, with specific action against Candida (Monilia) albicans.

It acts to prevent the monilial overgrowth which frequently occurs whenever tetracycline or any other broad spectrum antibiotic is used.

It protects your patient against antibiotic-induced intestinal moniliasis and its complications, including vaginal and anogenital moniliasis, even potentially fatal systemic moniliasis.

MYSTECLIN-V

Squibb Tetracycline Phosphate Complex (Sumycin) and Nystatin (Mycostatin)











LEAVES NOTHING TO BE DESIRED

HYCOMINE

THE COMPLETE Rx FOR COUGH CONTROL

cough sedative / antihistamine / expectorant

- relieves cough and related symptoms in 15-20 minutes
- effective for 6 hours or longer promotes expectoration
- · rarely constipates · cherry-flavored

Each teaspoonful (5 cc.) of HYCOMINE contains:

Hycodan®

Dihydrocodeinone Bitartrate 5 mg.) (Warning: May be habit-forming)	6.5 mg.
Homatropine Methylbromide 1.5 mg.	O.J IIIg.
Pyrilamine Maleate	
Ammonium Chloride	60 mg.
Sodium Citrate	85 mg.

Adult Dosage: one teaspoonful q. 6 h. May be habit-forming. Federal law permits oral prescription.



Literature on request

ENDO LABORATORIES Richmond Hill 18, New York

U. S. Pat. 2,890,400

ORINASE

BREAKTHROUGH IN DIABETES



ORINASE

BREAKTHROUGH IN DIABETES

Just last year, a new chapter began in the treatment of diabetes: Orinase became available for general clinical practice. Today, more than 300,000 diabetics are enjoying the advantages of oral management. This extensive experience, reinforcing the findings of hundreds of investigators in research centers all over the United States, has confirmed that Orinase is both safe and effective in the majority of adult, stable diabetics. And we now know that the significance of Orinase goes even further.

Before Orinase, research in diabetes was moving ahead slowly. Pathogenesis of the disease remained an enigma, and the mechanism of insulin action continued to elude investigators. Nor was any explanation forthcoming for the different types of diabetes mellitus, the progressive nature of the disease, or for the wide range of insulin requirements.

Clinically, too, there was much to be desired: the lifelong regimen of daily injections, the rigid meal schedules, and, above all, the constant threat of hypoglycemia. To the patient, these meant a life centered around his disease; to the physician, the ever-present danger of complications.

And now, one year after the introduction of Orinase, what has experience taught us? What has Orinase meant to practicing physicians, to patients, to investigators? What can we expect of the future? In briefest summary, this is where the evidence points:

Diabetes mellitus does not appear to be a single pathological entity. There are several types of diabetes mellitus. The most common is "Orinase-positive" diabetes, in which administration of Orinase induces release and utilization of the patient's endogenous insulin.

In "Orinase-positive" diabetics, Orinase achieves better control than injections of exogenous insulin.

ORINASE

ONE YEAR AGO-1957

Orinase was officially released for prescription on June 3, 1957. Prior to its release, it had been thoroughly and painstakingly tested in more than 20,000 patients.

severe trauma...gangrene...diabetes adequately

controlled by diet alone.

NUMBER OF PATIENTS ON ORINASE:	20,000
CRITERIA OF PATIENT SELECTION:	Adult, stable diabetes (onset around 40 years of age)
INCIDENCE OF SIDE EFFECTS: (transitory skin rash, nausea, etc.)	Only 3%
TOXICITY:	None
ESSENTIAL CONDITION FOR RESPONSE TO ORINASE:	Functional pancreas
MARY MODE OF ACTION OF ORINASE:	Unknown
CONTRAINDICATIONS:	Juvenile diabetesbrittle diabeteshistory of coma, acidosis, or ketosisfever

ONE YEAR LATER-1958

Today, Orinase is a routine therapeutic agent in the management of hundreds of thousands of diabetics. Numerous clinical observations confirm its efficacy and have brought to light many new, additional benefits of Orinase therapy.

Age: 40 + (at onset)
Insulin: 40 - (daily requirements)
These are typical criteria for the candidate most likely to respond to Orinase. However, diabetics with an earlier development of the disease also deserve a careful trial with Orinase, because Orinase has been found effective in many of the 20 to 40 age-of-onset diabetics.

Approximately 3% (side effects continue to be mild and transitory – drug withdrawn for these effects in only 1.6%)

None

Functional beta cells of the pancreas

In the presence of a functional pancreas, Orinase effects the production and utilization of native insulin via normal channels.

Juvenile diabetes...brittle diabetes...history of coma, acidosis, or ketosis...fever... severe trauma...gangrene...diabetes adequately controlled by dietary restriction alone.

Objective advantages of Orinase

Intensive diabetic research, stimulated by the introduction of Orinase, has led many investigators to revise the very concept of diabetes as a single clinical entity, and to coin the term "Orinase-positive" diabetes. Oral therapy of "Orinase-positive" diabetics presents the following advantages:

Better control of diabetes

Orinase-responsive patients show more stable blood sugar levels and less glycosuria on Orinase than on insulin. Because Orinase acts via *endogenous* insulin, daily control of diabetes is smoother; "peaks and valleys" typical of exogenous insulin are leveled out.

Greater freedom from hypoglycemia

Patients on Orinase rarely experience hypoglycemic reactions. Even when hypoglycemia does occur, it is milder and more amenable to therapy than insulin (hypoglycemic) reactions.

Side effects-few and minor

Side effects attributable to Orinase occur in about 3% of cases, and only half of these necessitate withdrawal of Orinase. Most common are skin rashes or mild G.I. upsets.

No known toxicity

Careful observations of large series of patients maintained on Orinase for more than two years revealed no damage to the liver, blood, kidneys, or pancreas. Orinase is not goitrogenic.

Painless management of diabetes

Simple, easy, oral administration eliminates subcutaneous fat atrophy and frequent allergic reactions to insulin.

No increase in insulin requirements

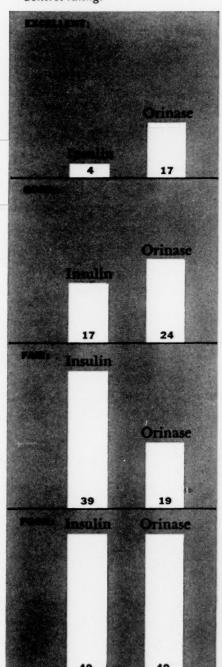
Even after prolonged Orinase therapy, patients scarcely ever show any increase in insulin requirements. In fact, such increase on Orinase is less common than on insulin.

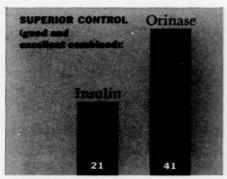
No impairment of diabetic status

Orinase therapy does not aggravate the underlying diabetic pathology. In some cases, there may be an actual improvement or even a remission.

QUALITY OF DIABETIC CONTROL IN 100 PATIENTS ON ORINASE COMPARED WITH CONTROL ON INSULIN¹

Control rating:

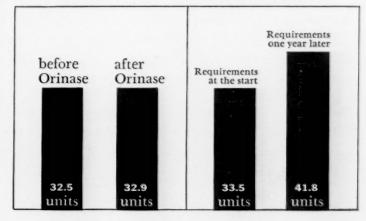




BETTER CONTROL OF DIABETES WITH ORINASE

NO INCREASE IN INSULIN REQUIREMENTS ON ORINASE²

Change in average insulin requirements of 30 diabetics resuming insulin after 1-15 months on Orinase Change in average insulin requirements of 100 diabetics after one year of insulin alone



- 1. Based on the data of McKendry, J. B. R.; Kuwayti, K., and Sagle, L. A.: Canad. M. A. J. 77:429 (Sept. 1) 1957.
- 2. Based on the data of Pfeiffer, E. F.: J. Endocrinol. 15:xlviii (June) 1957.

Subjective advantages of Orinase

"The extreme satisfaction of patients whose conditions are now controlled with tolubutamide is immeasurable."

Breneman, J. C.: J.A.M.A. 164:627 (June 8) 1957.

ORINASE HELPS TO CORRECT MAJOR DISLOCATIONS IN THE LIFE PATTERN OF DIABETICS

Orinase tends to restore emotional balance

Diagnosis of diabetes, usually coming late in life and carrying with it a long sentence of daily fear and anxiety, profoundly upsets the emotional balance of the average patient. Adjustment to radical changes in daily living is difficult. Daily injections, special meal schedules, and new limitations on activities make the patient feel "set apart." Oral therapy simplifies life, brings it closer to normal, helps restore a cheerful, hopeful outlook.

Sense of personal freedom regained on Orinase

No longer tied to a refrigerator, sterilizing apparatus, nearest restaurant, and rigid schedules, a diabetic on Orinase can enjoy travel and a variety of personal activities, free from the tyranny of the clock and the threat of hypoglycemia.

Orinase makes diabetes easier on the patient's family

With no dependence on members of the family for diabetic care, the patient can resume a more normal place in the family circle.

Orinase permits occupational continuity

Because of the hazards of hypoglycemic shock, some diabetics are forced to give up their customary occupations, or must limit and curtail their working hours—as may be the case with traveling salesmen, business executives, and others with unpredictable work schedules. On Orinase, patients usually can continue their normal occupations.

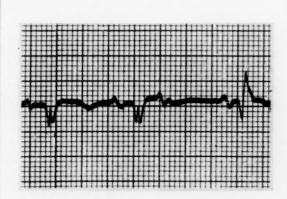
Normal social life made possible by Orinase

"Orinase-positive" diabetics can visit their friends, without the embarrassing necessity of meals at special hours...can participate in community life and social events in a more normal fashion.

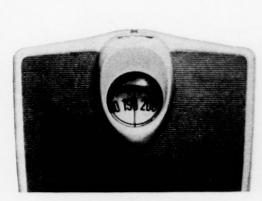
Stability and sense of well-being on Orinase

Patients report an increased sense of stability and well-being...they are less irritable...their mood and outlook are improved.

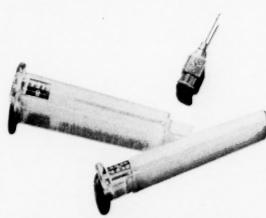
ADDED ADVANTAGES OF ORINASE IN DIABETICS WITH SPECIAL PROBLEMS



IN THE DIABETIC WITH CARDIOVASCULAR COMPLICATIONS, Orinase helps avoid superimposed hypoglycemic stress



IN THE OBESE DIABETIC, Orinase helps reinforce dietary discipline



IN THE DIABETIC WITH FEAR OF INJEC-TIONS, Orinase affords greater equanimity through oral control



IN THE DIABETIC WITH HYPERTENSION, Orinase reduces the pressure of rigid schedules



IN THE DIABETIC WITH TREMOR, Orinase overcomes the possibility of inaccurate self-injection



IN THE DIABETIC WITH IRREGULAR WORK-ING HOURS, Orinase removes the "tyranny of the clock" from the patient's therapeutic regimen

A New Life in THE ORINASE EPOCH

J.D.-FEMALE-AGE 32

Jane D., a successful commercial artist, now 32 years of age, had a sudden onset of diabetes in her early twenties after going through what seemed an



unduly prolonged and difficult recovery from a severe infection. At that time, she also experienced concomitant emotional upsets. When the diagnosis of diabetes was confirmed by a fasting blood sugar of 230 mg. per 100 cc. and 4 plus sugar in the urine, Jane was placed on 40 units of NPH insulin in the morning, and 5 units at night to prevent noc-



turnal hyperglycemia. She was ordered to maintain a restricted diet. Good control was established after a few hypoglycemic episodes secondary to disruption of her meal schedule.

When she returned to her drawing board after her illness and began her diabetic regimen, Jane found that her ability to function was impaired. She "felt ashamed" of her diabetes and refused to discuss it with anyone. She described herself as "limited emotionally" in both her business and social life. She "cheated" on



her diet and suffered accordingly, physically and psychologically. Because her work as an artist required her to conform to demands of clients for business meetings at odd hours and to complete assignments on rigid deadlines, she found herself under increasingly

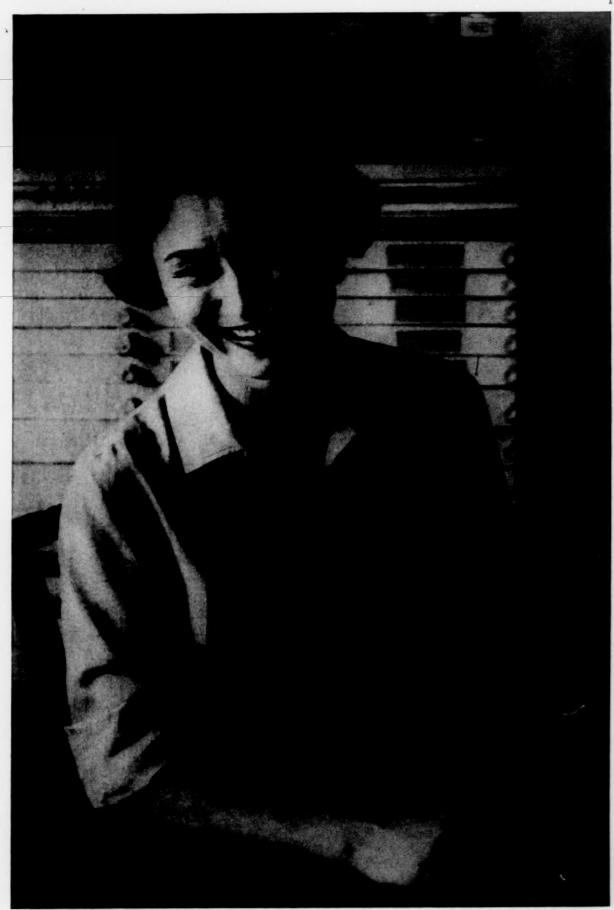
severe tensions. These, and her somewhat exaggerated fears of possible hypoglycemic reactions, carried over into her social activities as well.

The transfer to Orinase

Ten months ago, Jane's physician successfully transferred her from insulin to oral control with Orinase, establishing excellent balance on 0.5 Gm. t.i.d. Although she had become inured to her insulin injections, she found other factors in the oral medication providing definite advantages: less effort; emotional release from many of her former fears and tensions; greater freedom to work on irregular schedules; and ability to confront possible disruption of her mealtime.

Jane D. now leads a more normal existence. She is able to work consistently despite her irregular schedule. She is more relaxed in all her activities, and finds that her "consciousness of diabetes" has been virtually eliminated.

This case, illustrating some of the changing aspects of diabetes control offered by oral management, is based on actual clinical data.



THE ORINASE EPOCH

BREAKTHROUGH FOR THE PATIENT

A more normal, more secure life for the majority of diabetics.

BREAKTHROUGH FOR THE PHYSICIAN

Smoother control, free from the danger of hypoglycemic shock.

BREAKTHROUGH FOR METABOLIC INVESTIGATORS

New stimulus and new evidence in searching for the final answers to diabetes.

Dosage: Patients responsive to Orinase may begin therapy as follows:

3 Gm. First day Second day ... 2 Gm. Third day ... 1 Gm. Third day

Usual maintenance dose 1 Gm.

To change from insulin to Orinase: If previous insulin dosage was less than

40 u./day

reduce insulin 30% to 50% immediately; gradually reduce insulin dose if response to Orinase is observed.

40 u./day

more than reduce insulin 20% immediately; carefully reduce insulin beyond this point if response to Orinase is observed. In these patients, hospitalization should be considered during the transition period.

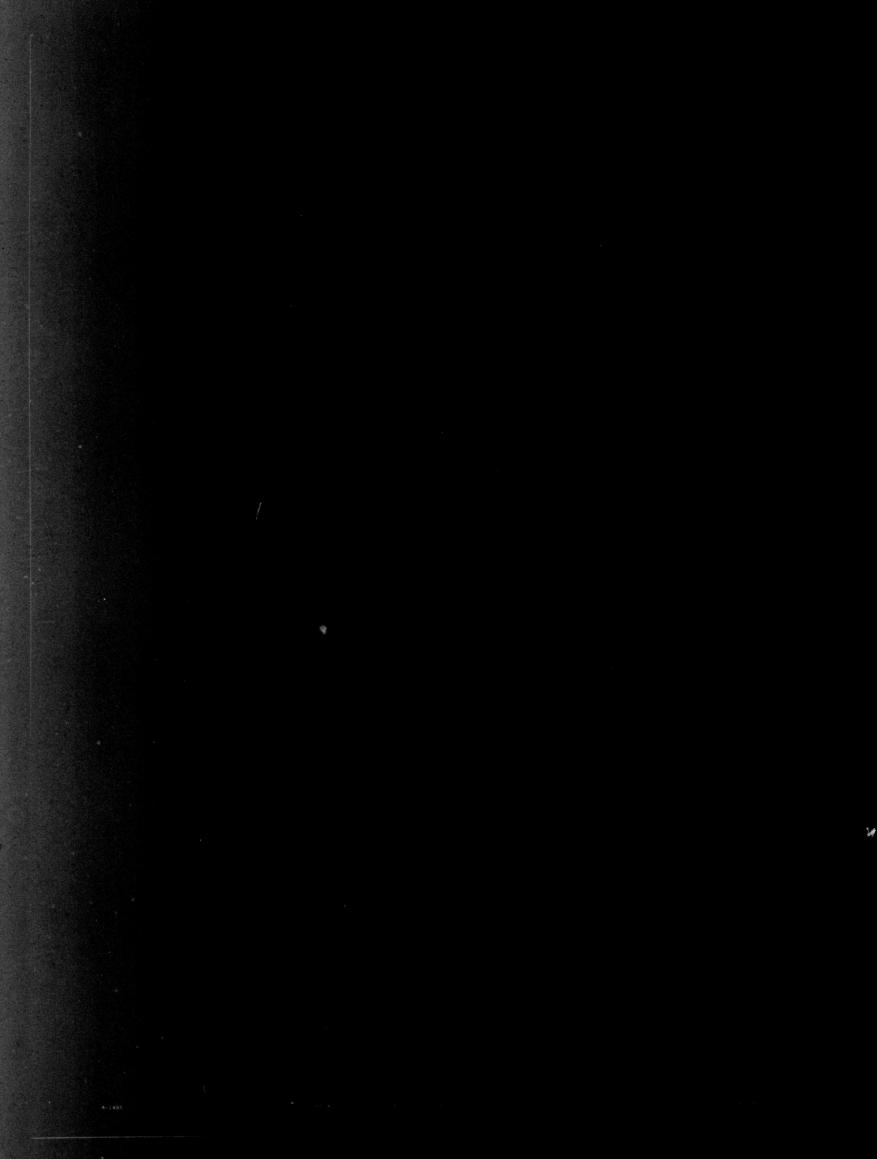
Prior to using Orinase in selected patients, the physician should perform a complete physical examination and indicated laboratory studies. During the initial test period, the patient should report to the physician daily, and for the first month at least once weekly for physical examination and blood sugar determination. After the first month, the patient should be examined at monthly intervals or more frequently as indicated.

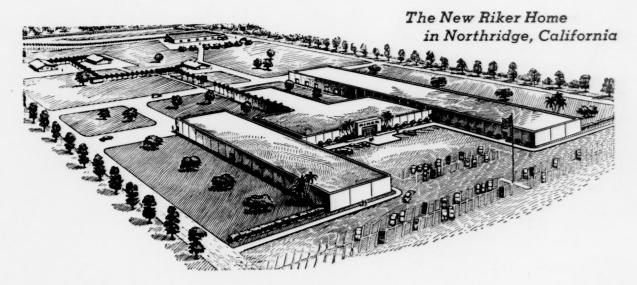
The patient should be instructed to report immediately to his physician if he does not feel as well as usual.

It is especially important that the patient, because of the simplicity and ease of administration of Orinase, does not develop a careless attitude ("cheating" on his diet, for example) which may result in serious consequences and failures of treatment.

Supplied: In 0.5 Gm. scored tablets, bottles of 50.







The Better to Serve The Profession

RIKER'S STAR has risen fast. In eight short years Riker has become recognized the world over as a source of advancements in pharmacologic therapeutics. This achievement is no accident; from the beginning the privilege of serving the profession has been considered a profound

obligation. Each Riker product, in order to qualify for the mark of "Another Riker First," has had to fulfill two basic requirements: It must represent a contribution to the field of therapeutics, and it must meet the strictest tests for efficacy, safety, standardization, and quality.

Riker Firsts:

Deaner®

a totally new molecule for the treatment of mild mental depression, fatigue, chronic headache, and psychoneuroses, as well as behavior and learning problems of children; distinguished for its freedom from pressor activity, skeletal muscle stimulation and other side actions.

Disipal®

an antiparkinson drug developed by Brocades-Stheeman of Holland. Its skeletal muscle-relaxant action was realized through Riker Research.

Medihaler®

the first means for administering self-propelled, automatical-

* Trademark of Brocades-Stheeman and Pharmacia. U.S. Patent No. 2,567,351. Other Patents pending. ly-measured-dose aerosol medications. Medihaler-Epi and Medihaler-Iso are unsurpassed in the treatment of asthma and allied pulmonary conditions. Medihaler-Phen relieves nasal congestion in common cold and in a variety of allergic conditions of the paranasal sinuses.

Rauwiloid®

the first Rauwolfia product developed and marketed in the United States. Known generically as the alseroxylon fraction of Rauwolfia serpentina, Benth., Rauwiloid was the first purified selective alkaloidal extract obtained from Rauwolfia. Rauwiloid is the basis for five Riker products used in cardiovascular and mental diseases.

Veriloid®

the first alkaloidal extract from Veratrum viride standardized for predictable therapeutic results in hypertension. Veriloid ushered in the era of modernday antihypertensive drugs. It is the basis for six Riker products.

Versenate,®** Calcium Disodium

specific therapy for acute lead poisoning.

** Trademark of the Dow Chemical Co.

Many other "Riker Firsts" are in Riker's future plans. It is our hope that each one will contribute to the prolongation of useful life and to the alleviation of suffering.





Oatmeal | Merits

Preference

The large number of breakfast cereals available may well give the erroneous impression that they are all more or less alike, and that the choice of one over the other is merely for the sake of variety.

Nothing could be further from the truth.

Oatmeal merits its position as a breakfast cereal widely recommended by physicians because it presents notable advantages.

First, oatmeal is known to provide more good quality protein than any other whole-grain cereal.

Next, oatmeal requires no fortification; it ranks highest among whole-grain cereals in thiamine and is significant in its content of other B vitamins and important minerals.

Just as important to the physician who prescribes a cereal food is oatmeal's inviting warmth, its delicious nut-like flavor, its ease of digestion, and the ready availability of its contained nutrients. Whether it be for an infant's first solid feeding...for the geriatric patient...for patients with gastrointestinal problems...and in many other situations, oatmeal makes a real contribution to the day's nutritional needs.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

The Quaker Oats Company





Doctors, too, like "Premarin"

THE doctor's room in the hospital is used for a variety of reasons. Most any morning, you will find the internist talking with the surgeon, the resident discussing a case with the gynecologist, or the pediatrician in for a cigarette. It's sort of a club, this room, and it's a good place to get the low-down on "Premarin" therapy.

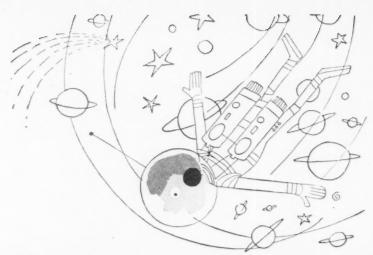
If you listen, you'll learn not only that doctors like "Premarin," but why they like it.

The reasons are simple. Doctors like "Premarin," in the first place, because it really relieves the

symptoms of the menopause. It doesn't just mask them—it replaces what the patient lacks—natural estrogen. Furthermore, if the patient is suffering from headache, insomnia, and arthritic-like symptoms due to estrogen deficiency, "Premarin" takes care of that, too.

"Premarin," conjugated estrogens (equine), is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

Ayerst Laboratories • New York 16, N. Y. Montreal, Canada



BRING HIM BACK FROM OUTER SPACE

to feed the inner man



With REDISOL (vitamin B_{12})—new zest for meals. Soluble REDISOL tablets (25, 50, 100, 250 mcg.) and cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) mix readily with liquids.

REDISOL is a trade-mark of Merck & Co., Inc.



MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

Pentoxilon

- Reduces incidence of attacks
- · Reduces severity of attacks
- · Reduces or abolishes need for fast-acting nitrites
- · Reduces tachycardia
- Reduces blood pressure in hypertensives, not in normotensives
- Increases exercise tolerance
- Produces demonstrable ECG improvement
- · Exceptionally well tolerated

Gives new courage to the anginal patient because it relieves anxiety and provides prolonged coronary vasodilatation.

Fear of the next attack is replaced by pulse-slowing, pleasantly tranquilizing effects which lessen severity and frequency of anginal attacks.

DOSAGE: One to two tablets q.i.d., before mea's and on retiring.



NORTHRIDGE, CALIFORNIA



Of course, women like "Premarin"

THERAPY for the menopause syndrome should relieve not only the psychic instability attendant the condition, but the vasomotor instability of estrogen decline as well. Though they would have a hard time explaining it in such medical terms, this is the reason women like "Premarin."

The patient isn't alone in her devotion to this natural estrogen. Doctors, husbands, and family all like what it does for the patient, the wife, and the homemaker.

When, because of the menopause, the psyche needs

nursing — "Premarin" nurses. When hot flushes need suppressing, "Premarin" suppresses. In short, when you want to treat the whole menopause, (and how else is it to be treated?), let your choice be "Premarin," a complete natural estrogen complex.

"Premarin," conjugated estrogens (equine), is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

Ayerst Laboratories • New York 16, N.Y. Montreal, Canada



"... Well, I usually prescribe Rorer's Maalox. It's an excellent antacid, doesn't constipate and patients like its taste better."

Maalox® an efficient antacid suspension of magnesium-aluminum hydroxide gel.

Suspension: Bottles of 12 fluidounces

Tablets: 0.4 Gram, Bottles of 100

Samples on request

WILLIAM H. RORER, INC., Philadelphia 44, Pennsylvania



The whole family likes "Premarin"

In a sense, when you prescribe "Premarin" for a wife and mother who is suffering in the menopause, chances are you're treating the whole family. Junior, Sis, and Dad, just like Mom, can tell the difference right off.

Mother isn't just more tranquil on "Premarin" therapy. Hundreds of published reports tell us she takes a positive outlook on life. She feels good. And we all know that's the single most important factor for a happy home.

Women on "Premarin" receive treatment that

covers every aspect of the menopause, including prompt relief of physical distress.

Is it any wonder physicians say the woman suffering in the menopause deserves "Premarin"? Many a family would agree.

"Premarin," conjugated estrogens (equine), a complete natural estrogen complex, is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

Ayerst Laboratories • New York 16, N. Y. Montreal, Canada

for profound vasodilation in acute vasospastic disorders

for prolonged vasodilation in chronic circulatory disorders

ILIDAR ROCHE

increases peripheral circulation and reduces vasospasm by (1) adrenergic blockade, Provides relief from aching, numbness, tingling, and blanching of the extremities. Exceptionally well tolerated.

and (2) direct vasodilation.

ILIDAR . BRAND OF AZAPETINE HOFFMANN-LA ROCHE INC . NUTLEY . N. J.





Husbands, too, like "Premarin"

The physician who puts a woman on "Premarin" when she is suffering in the menopause usually makes her pleasant to live with once again. It is no easy thing for a man to take the stings and barbs of business life, then to come home to the turmoil of a woman "going through the change of life." If she is not on "Premarin," that is.

But have her begin estrogen replacement therapy with "Premarin" and it makes all the difference in the world. She experiences relief of physical distress and also that very real thing called a "sense of well-being" returns. She is a happy woman again — something for which husbands are grateful.

"Premarin," conjugated estrogens (equine), a complete natural estrogen complex, is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

Ayerst Laboratories • New York 16, N. Y. Montreal, Canada





Back Issues Wanted

(MUST BE IN GOOD CONDITION)

THE AMERICAN JOURNAL OF MEDICINE

will pay \$1.00 per copy for the following issues:

January 1948

February 1948

March 1948

November 1948

May 1957

June 1957

August 1957

September 1957

November 1957

December 1957

May 1958

Send to

The American Journal of Medicine, Inc.

11 East 36th Street, New York 16, N. Y.

STATEMENT OF OWNERSHIP

STATEMENT REQUIRED BY THE ACT OF CONGRESS OF AUGUST 24, 1912, AS AMENDED BY THE ACTS OF MARCH 3, 1933, AND JULY 2, 1946 (Title 39, United States Code, Section 233) showing the ownership, management, and circulation of

The American Journal of Medicine, published monthly at New York, N. Y., for Oct. 1, 1958.

- 1. The names and addresses of the publisher, editor, managing editor, and business managers are: Publisher, The American Journal of Medicine, Inc., 11 E. 36th Street, New York 16, N. Y.; Editor, Alexander B. Gutman, M.D., Mount Sinai Hospital, 100th Street & Fifth Ave., New York 29, N. Y.; Managing Editor, Helena B. Mannion, 11 East 36th Street, New York 16, N. Y.; Business Manager, Pliny A. Porter, 11 East 36th Street, New York 16, N. Y.
- 2. The owner is: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual member, must be given.) The American Journal of Medicine, Inc., 11 East 36th Street, New York 16, N. Y.; M. T. Wisotzkey, President and Sole Owner, 11 East 36th Street, New York 16, N. Y.
- 3. The known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages, or other securities are: (If there are none, so state.) None,
- 4. Paragraphs 2 and 3 include, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting; also the statements in the two paragraphs shows the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner.
- 5. The average number of copies of each issue of this publication sold or distributed, through the mails or otherwise, to paid subscribers during the 12 months preceding the date shown above was:

(This information is required from daily, weekly, semiweekly, and triweekly newspapers only.)

M. T. WISOTZKEY, President

Sworn to and subscribed before me this 4th day of September, 1958.

Notary Public

[SEAL]
(My commission expires March 30, 1960.)

CARDIAC ARREST CAN OCCUR IN Your HOSPITAL ...

Each year about 10,000 patients face sudden death due to Cardiac Arrest.

> PM-65 with Electrocardioscope (optional) provides preventive detection and treatment of Cardiac Arrest.



For the possibility of Cardiac Arrest, whether on the operating table, during post-operative recovery, on the ward with Stokes-Adams patients, or in the Cardiac Catheterization Laboratory, Electrodyne presents proven* instruments that provide preventive detection of any Cardiac Arrhythmia and completely automatic treatment in cases of Cardiac Arrest.

*Developed in conjunction with Paul M. Zoll, M.D.

Other combinations and associated instrume available - Write for complete information

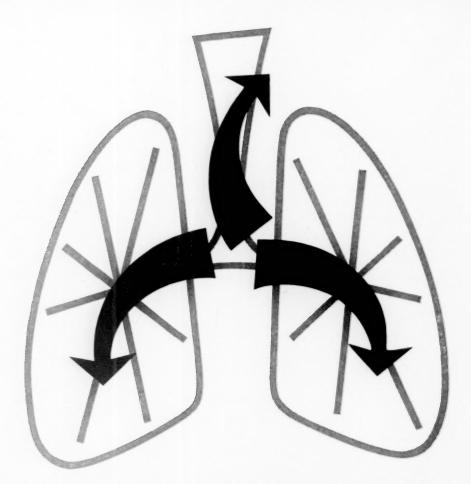


nd Defibrillator Model No. 43

Cardiac Alarm (Monitor) Model No. 54 — A visual and audible monitor which sounds alarm at onset of Cardiac Arrest.

Electrodyne Cardiac Defibrillator Model No. 33





3-way action helps asthma patients stay symptom-free

To keep your bronchial asthma patients symptom-free and on the job, an antiasthmatic must provide three therapeutic actions—bronchodilitation, vasoconstriction and mild sedation. Just such comprehensive control is available with Tedral.

Here is how each of Tedral's three ingredients acts specifically on a major symptom—

- 1. bronchial constriction relieved with theophylline (130 mg.)
- 2. mucous congestion reduced by ephedrine hydrochloride (24 mg.)
- 3. apprehension allayed with phenobarbital (8 mg.)

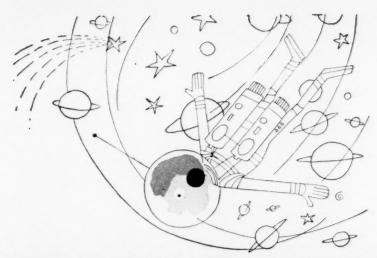
No single drug can equal Tedral in providing continuous protection against bronchial asthma symptoms.

dasage: 1 or 2 tablets every 4 hours. Tedral Enteric Coated (delayed action) administered together with Tedral (plain) at bedtime protects your patient all night.

Tedral

the dependable antiasthmatic MORRIS PLAINS. N.





BRING HIM BACK FROM OUTER SPACE

to feed the inner man



With REDISOL (vitamin B_{12})—new zest for meals. Soluble REDISOL tablets (25, 50, 100, 250 mcg.) and cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) mix readily with liquids.

REDISOL is a trade-mark of Merck & Co., Inc.



FEWER ANGINAL ATTACKS.
PROTECTS AGAINST PAIN
AND CONTROLS ANXIETY.
(EQUANIL AND PETN)

EQUANITRATE^{*}

Meprobamate and Pentaerythritol Tetranitrate

*Tradomark



Tablets: 炎衛家 6f-50, meprobamate (200 瑜虔) and pentaerythritol tetranitrate (10 mg.)



diaper rash?

DESITIN OINTMENT of course.*

*soothing, protective, anti-irritant Desitin®Ointment has been the answer for preventing and clearing up diaper rash in millions of babies for over 30 years.

We would be pleased to send SAMPLES on request.

DESITIN CHEMICAL CO., Providence 4, R. I.

which women...

and when...

need

iron therapy?



Many clinicians agree that the normal woman of child-bearing age requires iron therapy for a month or six weeks of *each* year.

Iron-deficiency anemia, usually identified as hypochromic microcytic anemia, is seen in most age groups, from the adolescent to the senior members.

For the treatment of these common anemias, Livitamin offers *peptonized* iron—virtually predigested, well absorbed, and less irritating than other forms. The Livitamin formula, which contains the B complex, provides integrated therapy to normalize the blood picture.

Formula: Each fluidounce contains:

Iron peptonize (Equiv. in ele	d eme	ent	ai	iro	on	i	7	420 mg.)
Manganese cit	rat	e, :	sol	ut	ole			158 mg.
Thiamine hydr	oct	ilo	rid	е				10 mg.
Riboflavin								10 mg.
Vitamin B ₁₂ Act (derived from								20 mcg.
Nicotinamide								50 mg.
Pyridoxine hyd	iroc	hle	ori	de				1 mg.
Pantothenic ad	cid							5 mg.
Liver fraction 1								2 Gm.
Rice bran extr								1 Gm.
Inositol								30 mg.
Choline								60 mg.
								-

LIVITAMIN®

with Peptonized Iron

To ensure desired
therapeutic response

e – look to peptonized iron



CURRENT STUDIES* SHOW PEPTONIZED IRON

One-third as toxic as ferrous sulfate.

Absorbed as well as ferrous sulfate.

Non-astringent.

Free from tendencies to disturb digestion. (One-tenth as irritating to the gastric mucosa as ferrous sulfate.)

More rapid response in iron-deficient anemias.

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

LIVITAMIN

with Peptonized Iron

CYCLOTHERAPY®



muscle spasm and joint pain... help alleviate



physical and nervous tension

Help in the relief of muscle spasm and the pains associated with spasm . . . when due to strains, minor sprains, bursitis, fibrositis, chronic or sub-acute arthritis and other musculoskeletal disorders . . . can be anticipated through the use of modern Cyclotherapy—a new concept in dynamic physiotherapy.

Basic Cyclotherapy units are therapeutic appliances that release a gentle, deeply penetrating, multi-directional force which "radiates" its revitalizing physical massage action through the soft tissue of the body, through bones and joints.

This action serves as a non-specific muscle relaxant with analgesic properties in connection with the above-mentioned syndromes. It also possesses non-specific sedative properties that help to relieve physical and nervous tension and encourages deep, natural sleep, in most people. This new dynamic physical modality lends itself to easy self-administration. It has been submitted to the most searching kind of clinical evaluation*—an evaluation which fully substantiates the information in this announcement.

FOR DETAILED INFORMATION AND DESCRIPTIVE LITERATURE, MAIL COUPON

CYCLOTHERAPY, INC. 11 East 68th Street, New York, N. Y.

*Medical Research data, descriptive literature available on request.

CYCLOTHERAPY, INC.
Dept. AMJ—118
11 E. 68th St., N. Y. 21, N. Y.
Would appreciate literature and full details on basic Cyclotherapy Units.

Name_____
Address_____
City_____State_____State_____

Vita-Metrazol

elixir and tablets

reactivates

A general tonic indicated in geriatrics, fatigue and senility — where apathy is the dominating symptom.

Contains Metrazol with selected vitamins.

Usual Dose: 1 or 2 tablets or teaspoonfuls of *Vita-Metrazol* 3 or 4 times daily.

Availability: Elixir in pint bottles, tablets in bottles of 100.

Metrazol®, brand of Pentylenetetrazol, E. Bilhuber, Inc.

KNOLL PHARMACEUTICAL COMPANY

ORANGI

Announcing

A handy, fully illustrated booklet containing reprints of all the articles of the

Symposium on Treatment of Myocardial Infarction

Price \$2.00

The American Journal of Cardiology, Inc.
11 East 36th Street
New York 16, N. Y.



pulse rate up?

Serpasil slows heart rate in most cases of organic or functional tachycardia.

You'll find it especially valuable in cardiac patients whose conditions are aggravated by heart speed-up. Through a unique heart-slowing action, independent of its antihypertensive effect, Serpasil prolongs diastole and allows more time for the myocardium to rest. Blood flow and cardiac efficiency are thereby enhanced.

What's more, you can prescribe Serpasil with confidence. Therapy with Serpasil is virtually free of the dangers (heart block and cardiac arrest) heretofore encountered with heart-slowing drugs. Side effects are generally mild and can be overcome by adjusting dosage.

DOSAGE FOR TACHYCARDIA Dose range is 0.1 to 0.5 mg. (two 0.25-mg. tablets) per day conveniently taken in a single dose. Rapid heart rate usually will be relieved within 1 to 2 weeks, at which time the daily dose should be reduced. Suppression of tachycardia often persists after therapy is stopped.

NOTE: In patients receiving digitalis or quinidine, Serpasil therapy should be initiated with especially careful observation. Serpasil is not recommended in cases of aortic insufficiency.

SUPPLIED: Tablets, 1 mg. (scored), 0.25 mg. (scored) and 0.1 mg. Elixits, 1 mg. and 0.2 mg. Serpasil per 4-ml. teaspoon.

slow it down with **Serpasil**

(reserpine CIBA)



Whenever a diagnostic "tool" can give you some added advantage in better performance or wider usefulness — your own diagnostic skill is aided by more complete facts, and your time is saved through simpler, more convenient use. Each of these Sanborn instruments gives you just such added advantages.

With the new Rappaport-Sprague Acoustic Stethoscope, sounds which are only faintly discernible or at the threshold of audibility with conventional stethoscopes become clearly audible, providing new assurance in auscultation. Equipped with five chest pieces for sensing and localizing sounds of various pitch, and three sets of ear pieces for proper fit, this new Stethoscope clearly reflects the results of ten years of research and investigation undertaken during its development.

In the Visette electrocardiograph, true portability in a clinically accurate ECG is now a practical reality. By its brief case size and 18-pound weight, the Visette lets you take 'cardiography to your patient — in his home, at the

hospital, at an industrial plant clinic, wherever the need exists. Modern electronic components — a new, much lighter galvanometer — design innovations ranging from pushbutton grounding and double-check standardization signals to fully automatic stylus stabilization as leads are switched — make the Visette the most convenient ECG you (and your technician) can use. And this first (and still the only) 18-pound 'cardiograph is now being used by more than 3000 doctors, both here and abroad.

For the benefits modern instrumentation can give you and your patients — by extending your diagnostic abilities and saving your time in day-to-day practice — ask your local Sanborn man for complete facts on these two unusual instruments. He will also be glad to tell you how you may use a Visette for 15 days in your own practice without cost or obligation, through the exclusive Sanborn "Try-Before-Buying" plan. Call or write him soon — or address Inquiry Director at the main office in Waltham, Mass.

SANBORN



COMPANY

MEDICAL DIVISION 175 Wyman Street,

Waltham 54, Massachusetts



Avoids Mental Cloudiness in hypertension therapy

Rautensin (the alseroxylon fraction of Rauwolfia) offers simple, safe, effective and easy-to-manage therapy for the complex problem of hypertension. Rautensin produces a gradual and sustained drop in blood pressure ... calms and soothes the anxious patient without loss of alertness...slows accelerated pulse. Patients on this regimen show marked reduction of anxiety with a simultaneous increase in intellectual and psychomotor efficiency.1

With the use of the alseroxylon fraction of Rauwolfia, side actions "... are either completely absent or so mild as to be inconsequential" and there is "...no danger of sudden rebound of the blood pressure."2 Furthermore, alseroxylon was found less prone to cause mental depression, and does not usually cause drowsiness. Rautensin is purified and therefore free of inert dross present in the whole root.

- Wright, W. T. Jr.; Pokorny, C., and Foster, T. L.: J. Kansas M. Soc. 57:410, 1956.
 Terman, L. A.: Illinois M.J. 3:67, 1957.
 Moyer, J. H.; Dennis, E., and Ford, R.: Arch. Int. Med. 96:530, 1955.

Rautensin®

The purified alkaloid complex of Rauwolfia with total therapeutic activity-minimal side effects. Each tablet contains 2 mg. purified Rauwolfla serpentina alkaloids (alseroxylon fraction)



Portland physicians find that Serpasil® does more than reduce high blood pressure

Physicians in Portland, Maine, have found that Serpasil has advantages beyond its antihypertensive action:

- 1. With its rather pronounced central effect Serpasil calms patients who are frankly anxious or tense, as well as hypertensive.
- 2. The heart-slowing action of Serpasil relieves the tachycardia that so often complicates high blood pressure.

These facts were brought out by 450 U.S. physicians who were interviewed in a worldwide survey* conducted by CIBA. They reported that 74 per cent of 871 patients

treated with Serpasil for hypertension with anxiety-tension had excellent or good overall response, while 80 per cent of 261 patients treated for tachycardia had good or excellent response.

Their experience offers good reason to prescribe Serpasil whenever marked anxietytension or tachycardia accompany high blood pressure.

SERPASIL® (reserpine CIBA)

C I B A SUMMIT, N. J.

*Complete information about the results of this survey will be sent on request.

Index to Advertisers

November, 1958

Abbott Laboratories													In.	sert	Faci	ing .	Page 50
Ames Company, Inc.																	4, 70
Ayerst Laboratories		32,	68	-69	, 92	-93	3, 1	09,	111	, 11	3,	115	, In.	sert	Faci	ng .	Page 40
Burroughs Wellcome & Co., Inc																	77
Ciba Pharmaceutical Products, Inc.								26,	47,	52,	75,	91,	123	3, 12	26, I	Four	th Cove
Corn Products Refining Company.																	17
Cyclotherapy, Inc																	121
Desitin Chemical Company																	120
Eaton Laboratories																	16
Electrodyne Co., Inc												*					117
Endo Laboratories																6	96
Irwin, Neisler & Co																	40
Kinney & Company, Inc																	56
Knoll Pharmaceutical Company																	122
Lakeside Laboratories, Inc																	57
Lederle Laboratories Division, America	n (Cya	ına	mid	Co	mp	oan	y					12,	21,	35,	58.	, 84-85
Eli Lilly and Company																	64
Lloyd Brothers, Inc.																	70
The S. E. Massengill Company																	age 120
McNeil Laboratories, Inc.															53-	-54-	-55, 73
Mead Johnson																10-	-11, 78
Merck Sharp & Dohme		14	-15	5, 2	2-2	3, 2	27,	29,	40,	42,	72	, 74	, 86	-87	, 89	, 11	10, 119
The Wm. S. Merrell Company																	80-81
Nordson Pharmaceutical Laboratories,	Inc																82-83
Organon Inc.										,							36
Parke, Davis & Company														28,	33,	60-	-61, 71
Pfizer Laboratories, Division of Chas. P	fize	er &	8: (Co.,	Ind									8,	37,	38,	50-51
The Quaker Oats Company																	108
Riker Laboratories Inc.												34,	107	, 11	0, 7	Thir	d Cover
A. H. Robins Co., Inc																	29, 59
Roche Laboratories, Div. of Hoffmann-	La	Ro	och	e I	nc.								. 4	13-4	4-4	5-4	16, 114
William H. Rorer, Inc.																	112
Sanborn Company																	124
Schenlabs Pharmaceuticals, Inc.		-															13, 88
Schering Corporation																	31
G. D. Searle & Co																٠	65
Sherman Laboratories																	90
Smith-Dorsey, a Division of the Wander																	125
Spirit & Co., Inc.																	72
E. R. Squibb & Sons, Division of Math	ieso	on	Ch	emi	cal	Co	rp.					6,	62-	63,	66,	79,	94-95
Sunkist Growers																	
The Upjohn Company . 97-98-99-100)-1	01-	-10	2-1	03-	104	1-1	05-	106	Ins	erts	Fac	cing	Pag	jes 9	6 a	nd 106
Wallace Laboratories													9,	18-	19,	24,	41, 67
Warner-Chilcott Laboratories																67	
White Laboratories, Inc.																	25
Winthrop Laboratories																	
Wyeth Laboratories												20	1. 2	7. 3	9. 4	9.8	9, 119



Mrs. H. T., a 30-year-old housewife, bore her first child at 26 years of age. After the deliveryand now for full four years-she has been unable to shed the excess pounds gained during pregnancy. Complete amenorrhea persisted for a year after birth, followed by only gradual return to more normal menses. Despite a seemingly healthy appearance, Mrs. H. T. suffers from exhaustion. Her memory is poor; she is not alert. Since the baby's birth, she has not regained her complete strength. "I feel cold all the time," she complains. "My skin and hair are dry."

PBI is 2.0 mcg.%; BMR -33; cholesterol 385 mg.%; EKG of reduced amplitude.

Based on history and findings, a diagnosis of hypothyroidism is made and thyroid substitution (3 gr. Proloid daily) prescribed. Within 4 months, her PBI rose to 5.4 mcg.%; cholesterol fell to 242; and EKG returned to normal. In view of the favorable results, therapy is continued indefinitely.

pattern of SUBCLINICAL HYPOTHYROIDISM

Highly purified natural thyroid extract, Proloid provides all the fractions of thyroid secretion to normalize every facet of thyroid function.

Double assay—chemical and biological—assures a predictable clinical response for safe, effective long-term therapy. Proloid is available in 5 tablet sizes: 1/4, 1/2, 1, 11/2 and 5 grain tablets—and Proloid Powder for compounding.

PROLOID®

the total thyroid complex





Many such
hypertensives have
been on Rauwiloid
for 3 years
and more*

for Rauwiloid IS better tolerated...
"alseroxylon [Rauwiloid] is an antihypertensive agent of equal therapeutic efficacy to reserpine in the
treatment of hypertension but with
significantly less toxicity."

*Ford, R.V., and Moyer, J.H.: Rauwolfia Toxicity in the Treatment of Hypertension, Postgrad. Med. 23:41 (Jan.) 1958.

For gratifying Rauwolfia response

Rauwiloid

ALSEROXYLON, 2 MG

virtually free from side actions

Enhances safety when more potent drugs are needed.

Rauwiloid* + Veriloid*

obseroxylon 1 mg. and alkovervir 3 mg. for moderate to severe hypertension. Initial dose, 1 tablet t.i.d., p.c.

Rauwiloid* + Hexamethonium

alseraxylon 1 mg. and hexamethonium chloride dihydrate 250 mg.

in severe, otherwise intractable hypertension. Initial dose, ½ tablet q.i.d. Both combinations in convenient single-tablet form. just two tablets at bedtime

After full effect one tablet suffices

